Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Austria, and co-rapporteur Member State, the Czech Republic, for the pesticide active substance pethoxamid 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 pethoxamid as a herbicide on maize and soya bean. The reliable endpoints, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as ‘the Regulation’) lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Pethoxamid 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), Austria, and co-rapporteur Member State (co-RMS), the Czech Republic, received an application from Cheminova A/S for the renewal of approval of the active substance pethoxamid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Czech Republic), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on pethoxamid in the renewal assessment report (RAR), which was received by EFSA on 31 August 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Cheminova A/S, for comments on 27 October 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 5 January 2017.

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

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

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

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

In the area of identity, physical/chemical properties and analytical methods, a data gap was identified for a monitoring method of the compounds of the residue definition in groundwater.

For the mammalian toxicology chapter, the assessment of the toxicological profile of the dietary metabolite MET-30 was identified as a data gap. The lack of in vitro comparative metabolism data and the endocrine disruption potential of pethoxamid (regarding the scientific risk assessment) were indicated as issues that could not be finalised.

In relation to the residues in food and feed, enough data are available to establish a residue definition and perform a risk assessment for the primary crops maize and soya bean. Maximum residue level (MRL) proposed at the limit of quantification (LOQ) for the parent pethoxamid is confirmed by the available data. However, for succeeding crops/additional crops (leafy and fruits) that will be grown after a crop failure, a data gap has been identified for additional information on rotational crops residues, to avoid a risk resulting from residues of MET-30 and other potential metabolites. The preliminary definition of residues for rotational crops for risk assessment is parent pethoxamid and MET-30, pending also on further information on the toxicity of this metabolite. Consequently, the consumer risk assessment cannot be concluded at this stage. Exposure through livestock products is not expected as a result of the representative uses proposed. Finally, a data gap on residue levels in pollen and bee products for human consumption is identified.

With respect to the fate and behaviour in the environment, enough information is available to perform the exposure assessment. A critical area of concern has been identified in relation to potential groundwater contamination by aerobic soil metabolites MET-42, MET-101 and MET-100, considered relevant based on the available mammalian toxicology information and the pertinent guidance on assessing the relevance of groundwater metabolites. A data gap was identified for the submission of appropriate information addressing the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. This resulted in the consumer risk assessment from drinking water being not finalised.

In the area of ecotoxicology, data gaps were identified for further information to address the risk to aquatic organisms and honeybees for pethoxamid and its metabolites. A data gap was identified for further information to address the risk to earthworms for MET-101.
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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 of an 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 Austria and co-RMS the Czech Republic received an application from Cheminova A/S for the renewal of approval of the active substance pethoxamid. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Czech Republic), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on pethoxamid in the RAR, which was received by EFSA on 31 August 2016 (Austria, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Cheminova A/S, for consultation and comments on 27 October 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 5 January 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant’s response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 16 February 2017. On the basis of the comments received, the applicant’s response to the comments and the RMS’s evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

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

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

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in July-August 2017.

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

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\(^{1}\) 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.
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 (16 February 2017);
- the evaluation table (22 August 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 (Austria, 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 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**

Pethoxamid is the ISO common name for 2-chloro-N-(2-ethoxyethyl)-N-(2-methyl-1-phenylprop-1-enyl)acetamide (IUPAC).

The representative formulated product for the evaluation was ‘CHA 2745-02’, an emulsion concentrate (EC) containing 600 g/L pethoxamid.

The representative uses evaluated were by spray application against mono- and dicotyledonous weeds in soya beans (pre-emergence) and in maize (both pre-emergence and early post-emergence). Full details of the representative uses can be found in the list of end points in Appendix A.

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

**Conclusions of the evaluation**

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

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

The new proposed specification for pethoxamid is based on batch data from industrial scale production. The proposed minimum purity of the technical material is 945 g/kg. There is no FAO specification available for pethoxamid. Toluene is considered a relevant impurity, however of no toxicological concern at the level specified (maximum 3 g/kg). The batches used in the (eco)toxicological assessment support the proposed renewal specification (see Section 2).

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 pethoxamid or the representative formulation. The main data regarding the identity of pethoxamid 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 and the relevant impurity in the technical material and in the representative formulation.

Pethoxamid residues can be monitored in food and feed of plant origin by the QuEChERS method using liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a limit of quantification (LOQ) of 0.01 mg/kg in each commodity group. A LC–MS/MS method exists for monitoring pethoxamid residues in food of animal origin with a LOQ of 0.01 mg/kg in all animal matrices. However, the residue definitions for rotational crops and animal products are currently open (see Section 3) and additional monitoring methods might be required should new components be included in the residue definitions.
Pethoxamid residues in soil and surface water can be monitored by LC-MS/MS with a LOQ of 0.01 mg/kg and 0.10 μg/L, respectively. However, the residue definition for soil and surface water is considered open (see Appendix A) and additional monitoring methods might be required should new components be included in the residue definition. The residue definition for monitoring in groundwater was concluded as pethoxamid, MET-42, MET-101, MET-100 and MET-22 (see Section 4). As a consequence, a data gap for a monitoring method in groundwater was identified. An appropriate LC-MS/MS method exists for monitoring pethoxamid residues in air with a LOQ of 6.0 μg/m³.

The LC-MS/MS method can be used for monitoring pethoxamid residues in body fluids with a LOQ of 0.05 mg/L. The method for monitoring of pethoxamid in food of animal origin can be used for determination of pethoxamid in body tissues.

2. Mammalian toxicity

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

Pethoxamid has been discussed during the Pesticides Peer Review experts’ meeting 159 (June 2017). The batches used for the toxicological studies can be considered as representative of the new technical specification. Toluene is considered a relevant impurity. No evaluation of the representativeness of the toxicological batches to the original reference specification was available.

With an oral absorption value > 80%, the highest concentrations of pethoxamid were measured in tissues responsible for metabolism and excretion (gastrointestinal tract, liver and kidneys), with indication of a possible binding to red blood cells. Mainly eliminated via bile and urine, pethoxamid did not show any bioaccumulation potential and was extensively metabolised to cysteine conjugates, sulfoxides and sulfones. Comparative in vitro metabolism (for animal species used in pivotal studies and human material, microsomes or intact cell systems) cannot be concluded on the basis of the available data leading to a data gap and an issue that could not finalised.

Pethoxamid is of moderate acute toxicity via the oral route (harmonised classification Acute Tox 4, H302) and of low acute toxicity via the dermal and inhalation routes. Without skin or eye irritating properties, it is, however, classified as a skin sensitisser (harmonised classification Skin Sens 1, H317) may cause an allergic skin reaction; proposed subcategorisation to 1A). No phototoxic hazard was identified in an acute in vitro phototoxicity study.

In short-term toxicity studies with rats and mice, adverse effects are observed in the liver and thyroid at high dose levels. Effects in the gastrointestinal tract were also observed in mice and dogs. The relevant no observed adverse effect level (NOAEL) for rats is 7.5 mg/kg body weight (bw) per day based on decreased body weight gain and food consumption, whereas the relevant NOAEL for mice is 70 mg/kg bw per day based on decreased body weight gain and effects in liver and thyroid. In dogs, the relevant NOAEL is 2 mg/kg bw per day based on increased liver weight and clinical signs (diarrhoea) in the 1-year study.

On the basis of the available data, pethoxamid is concluded as unlikely to be genotoxic.

For the long-term toxicity study with rats, the thyroid weight increase at the low dose was not considered adverse (due to its transient nature, not dose-related, and considering the high variability in organ weights), and the relevant NOAEL is 1 mg/kg bw per day based on decreased body weight gain in females. For the 18-month mouse study, treatment-related effects included histopathological findings in the duodenum, jejunum, kidney, liver and thyroid, triggering a lowest observable adverse effect level (LOAEL) of 4 mg/kg bw per day (based on swelling and rarefaction of villous epithelial cells in the duodenum of males).

Pethoxamid is listed in Annex VI of Regulation (EC) 1272/2008 and no classification for carcinogenicity is included. The carcinogenicity studies were available in the original dossier, but EFSA does not have information regarding the assessment of carcinogenicity by the European Chemicals Bureau regarding the consideration of the substance under the previous regulatory frame for classification and labelling. Thyroid tumours were observed in high dose rats and liver tumours were observed in high-dose mice. New mechanistic studies were provided to support a phenobarbital mode of action via an activation of the constitutive androstane receptor (CAR) in the nucleus (with induction of UDP-glucuronosyltransferase (UGT)). These data and the carcinogenic properties of pethoxamid

3 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1-1355.
thyroid tumours in rats and liver tumours in mice) were extensively discussed by the experts, mainly considering whether or not a phenobarbital mode of action was sufficiently demonstrated, and whether it can be considered relevant to humans or not. During the meeting, a slight majority of the experts considered that pethoxamid should not be classified as carcinogenic. After further consideration of the existing knowledge, the opinions were evenly divided in a post-meeting consultation. As a consequence, EFSA considers that the proposed classification\textsuperscript{4} Carcinogen category 2 should apply to pethoxamid. It is noted that the RMS disagreed and is of the opinion that classification for carcinogenic effects is not necessary.

In the rat multigeneration study, no adverse effect was observed on the reproductive parameters, and the parental and offspring NOAEL is 11 mg/kg bw per day based on decreased body weight (gain) and organ weight changes. For the assessment of developmental toxicity, new studies were provided and taken into consideration together with the original ones. The overall maternal NOAEL is 8 mg/kg bw per day in rats and 50 mg/kg bw per day in rabbits, while the overall developmental NOAEL is 75 mg/kg bw per day in rats and 12.5 mg/kg bw per day in rabbits. No teratogenic potential was detected for pethoxamid.

Pethoxamid is not classified or proposed to be classified as toxic for reproduction category 2, in accordance with the provisions of Regulation (EC) No 1272/2008, 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 considerations of endocrine disrupting properties are not met. Pethoxamid increased liver catabolism leading to increased thyroid hormone clearance. These adverse effects might be viewed as endocrine disruption potential. EFSA considers that on the basis of the available data and current knowledge it cannot be excluded that endocrine-mediated adverse effects following exposure to pethoxamid will be observed. The experts’ opinions were evenly shared, and half of them (including the RMS) did not support the EFSA view. EFSA considers that a data gap should be identified for further investigation of the endocrine disrupting properties of pethoxamid leading to an issue that could not be finalised.

No evidence of neurotoxicological finding was observed in an acute neurotoxicity study with rats.

The same reference values as those set during the first peer review (European Commission, 2006) were agreed for pethoxamid (with the application of an uncertainty factor (UF) of 100): an acceptable daily intake (ADI) of 0.01 mg/kg bw per day based on the 2-year rat study; an acceptable operator exposure level (AOEL) of 0.02 mg/kg bw per day based on the 1-year dog study, an acute reference dose (ARfD) and acute AOEL (AAOEL) of 0.08 mg/kg bw based on the developmental rat study supported by the 90-day dog and rat studies (based on body weight decrease already observed on week 1).

Based on the triple pack approach, the dermal absorption values are 2% for the concentrated product and 8% for the field dilution. Considering the representative use in maize (covering also soya bean crops), the operator exposure estimates are below the AOEL with the use of personal protective equipment (German model). Bystanders, residents, and workers re-entering for inspection purposes will also have exposure levels below the AOEL (Europoem II, German model, UK model).

For several metabolites, toxicological studies and quantitative structure-activity relationship (QSAR) analyses were provided and discussed by the experts. Groundwater metabolites MET-42, MET-100, MET-101 and MET-22 are all considered relevant since it cannot be excluded that they share the carcinogenic potential of pethoxamid leading to a critical area of concern (see Section 4). Reference values for MET-42 and MET-22 were agreed during the experts’ meeting. The data available were not sufficient to establish reference values for the metabolites MET-100 and MET-101; this was identified as a potential data gap, should it be demonstrated that the metabolites are not relevant (see Section 7). A data gap for the dietary metabolite MET-30 is identified to define its toxicological profile.

\section{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).

\textsuperscript{4} It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.
Pethoxamid was discussed at the Pesticides Peer Review experts’ meeting 161 (13–14 June 2017).

Metabolism of pethoxamid was investigated after foliar applications in root crops (potatoes), bare soil (pre-emergence) and foliar application in cereals/grass (maize) and pulses and oilseeds (soya bean) crop groups using pethoxamid 14C-labelled on the phenyl ring. Confined rotational crop metabolism studies in root/tuber crops (carrots), leafy crops (spinach) and cereals (wheat) were conducted with bare soil applications of pethoxamid 14C-labelled on the phenyl ring. Parent pethoxamid was observed in each of the crops, but only at early growth stages shortly after application. Pethoxamid was not observed in mature maize grain, soya beans or potato tubers. In all crops investigated, the metabolism of pethoxamid is initiated by glutathione conjugation through substitution of chloride. Subsequently, this conjugate is degraded to pethoxamid cysteine conjugate (MET-30). Residues of parent pethoxamid are not found in any plant parts soon after application. Pethoxamid by default is proposed as residue definition for risk assessment and monitoring of residues in plant products. This is acceptable for the grain and tuber products where practically no residues are found during metabolism studies. However, for succeeding crops/additional crops (leafy and fruits) that will be grown after a crop failure, additional information on rotational crops residues are considered necessary, to avoid a risk resulting from residues of MET-30 and other potential metabolites (data gap identified, see Section 7). Therefore, the residue definition for rotational crops for monitoring is proposed as parent pethoxamid only in general and considered open in case of leafy crops and fruits. The definition of residues for rotational crops for risk assessment is parent pethoxamid and MET-30 pending also on further information on the toxicity of this metabolite (see Section 2) and on the identification of other potential metabolites (data gap).

Effect of processing on residues was not investigated (not required) as no residues in crops exceeding 0.01 mg/kg are found in the available studies.

Results of the available studies show that residues of pethoxamid are generally not stable in samples of soya bean seed and oilseed rape stored at –20°C for more than 12 months. Stability of residues of samples in residue trials was discussed during the experts’ consultation, resulting in the exclusion of some of the available residue trials from the assessment. Nevertheless, sufficient residue trials remain as reliable to confirm a MRL of 0.01* mg/kg for maize grain and soya bean.

Metabolism studies in livestock are not triggered according to dietary burden calculations. However, metabolism studies in goat and laying hens have been submitted. No accumulation of residues in tissues despite the log \( P_{ow} \) close to 3 is expected since the hens study showed no indication for fat soluble residues. A residue definition for animal products can currently not be set since the toxicological relevance of a major metabolite in animal products (MET-30) would need to be addressed before a final conclusion could be derived on the pertinent residues in animal commodities. The RMS proposed parent by default but this would need to be reconsidered as well as the importance of conjugated parent residues, in case livestock dietary exposure becomes significant in future. As no feeding study is required, stability data in commodities of animal origin are also not necessary. A fish metabolism study was not provided and is not requested as pethoxamid residues in commodities relevant for fish feeding are below the LOQ of the method (0.01 mg/kg).

Information to address the residues in pollen and bee products was required during the peer review. While no residue data in pollen and bee products are available, the occurrence of residues above the LOQ in pollen and bee products cannot be excluded with certainty based on the available information. Although the applicant presented a risk assessment based on estimated total residues at flowering from available metabolism information and worst-case assumptions, showing that no significant increase of risk for consumers is expected from potential residues of pethoxamid in honey, the data are insufficient to assess the necessity of MRLs for pollen and bee products, and to numerically derive such MRLs as appropriate (data gap).

For the time being, consumer dietary risk assessment can only be conducted for parent pethoxamid residues in primary crops considering the outstanding data to address the magnitude and relevance of metabolites in leafy and fruit rotational crops. In this preliminary assessment, long-term or short-term intake concerns were not identified for consumers since the highest chronic and highest acute intakes accounted for 4.4% ADI (UK, toddler) and 1.9% ARF (potato). For leafy and fruit crops that can be grown in rotation, a data gap for the identification of further metabolites was identified. While MET-30 may need to be considered for the risk assessment of these crops, pending the provision of toxicological information (see Section 2), the consumer risk assessment cannot be concluded at this stage.

* MRL is proposed at the LOQ.
4. Environmental fate and behaviour

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions (10°C and 20°C) in the dark, pethoxamid exhibited low persistence while under anaerobic soil incubations pethoxamid exhibited moderate persistence. Under aerobic conditions pethoxamid forms the major or minor non transient metabolites MET-42 (max. 11.2% applied radioactivity (AR)), MET-101 (max. 9% AR) and MET-100 (max. 9% AR). In the additional anaerobic incubation, two further metabolites were identified: MET-22 (max. 8.8%) and MET-46 (max. 8.1%). Under aerobic conditions, these metabolites exhibited moderate to medium (MET-42), moderate to high (MET-101), low to medium (MET-100), moderate to medium (MET-22) and very low (MET-46) persistence, respectively. Under aerobic conditions at 20°C, mineralisation of pethoxamid accounted for 34.2-46.2% AR after 120 days. The formation of unextractable residues (not extracted by acetonitrile/water) accounted for 20.7-35.1% AR after 120 days. In anaerobic soil incubations, pethoxamid exhibited moderate persistence. Despite not being required, dissipation of pethoxamid was also investigated under field conditions in three field sites in the EU (one site in France and two in Spain, spray application to the soil surface on bare soil plots in late spring). Occurrence of metabolite MET-42 was also investigated in these trials. Pethoxamid exhibited moderate to medium persistence in these experiments. Normalisation of these field degradation data is not available. MET-42 was found in all three trials but no reliable kinetic formation and degradation parameters for the metabolite could be derived from the field data.

According to the results of the batch adsorption/desorption studies, it may be expected that pethoxamid would exhibit high to medium mobility in soil. MET-42 and MET-100 exhibited very high mobility, MET-22 exhibited high soil mobility.

In a field leaching study with one application of 1.2 kg a.s./ha and residues followed for 1 year in soil horizons down to 125 cm, pethoxamid in the leachate at 1 m depth was detected only in two samples (out of 175) at the level of 0.1 μg/L (LOQ of the method used). However, concentration of metabolite MET-42 were detected at levels > 0.1 μg/L in the majority of the samples and reached a maximum concentration of 11 μg/L in the leachate at 1 m depth.

Pethoxamid is stable to hydrolysis under environmental relevant pH values (pH = 4-9). Under aqueous photolysis conditions, simulating natural light pethoxamid degrades with a half-life of 7.7 days. Major aqueous photolysis metabolites are MET-102 (max. 21.5% AR) and benzoic acid (max. 31.6% AR). In laboratory incubations in dark aerobic natural sediment water systems, pethoxamid exhibited low to moderate persistence, forming the metabolites MET-6 (max. 9.4% AR) and MET-104 (max. 8.8% AR). The unextractable sediment fraction was the major sink for pethoxamid, accounting for 57.1-64.9% AR at study end (102 days). Mineralisation accounted for 13.4-16.3% AR at the end of the study. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC_SW/SED) calculations) were carried out for the parent and metabolites MET-42, MET-101, MET-100, MET-22, MET-46, MET-102, benzoic acid, MET-30, MET-6 and MET-104 using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1-2 in FOCUS calculator). For the active substance pethoxamid and metabolite MET-22, appropriate step 3 (FOCUS, 2001) calculations were available. In addition, exposure assessment of pethoxamid taking into account risk mitigation measures (20 m drift buffer zone + 20 m vegetated run off filter strip) was available to refine the risk assessment and was calculated using FOCUS Step 4 tools. For the step 4 calculations, wet and dry depositions were considered (to take into account short-range transport through air due to its medium volatility); however, their contribution was found marginal. 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 Kfoc < 2,000 mL/g (i.e. pethoxamid), 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.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models MACRO 5.5.4 (Châteaudun), PEARL 4.4.4 and PELMO 5.5.3 for the active substance pethoxamid and metabolites MET-42, MET-101, MET-100, MET-22 and MET-46 considering the representative use in maize. The potential for groundwater exposure from the representative uses by pethoxamid and anaerobic metabolite MET-46 above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all eight relevant FOCUS groundwater scenarios. For the anaerobic metabolite MET-22, simulations correctly utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

5 Simulations correctly utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.
there is the potential for exceeding the parametric drinking water limit of 0.1 \( \mu \text{g}/\text{L} \) in three to five of the eight scenarios. However, this is only expected to happen if prolonged anaerobic conditions were to occur in the locations with the identified vulnerable geoclimatic situations represented by those scenarios. For the representative uses on maize and soya bean, prolonged periods of anaerobic soil conditions might only be expected in limited areas and rarely. A high potential for groundwater contamination above the parametric drinking water limit of 0.1 \( \mu \text{g}/\text{L} \) in all eight relevant scenarios is identified for the aerobic metabolites MET-42, MET-101 and MET-100. The level of 0.75 \( \mu \text{g}/\text{L} \) is also exceeded in at least seven of the scenarios. In the case of the metabolite MET-42, the high potential for leaching has been confirmed by a higher tier field leaching study (even when this study has only run for a single year). Calculations assuming application every two years do not result in a majority of scenarios below the parametric drinking water limit of 0.1 \( \mu \text{g}/\text{L} \). Therefore, a critical area of concern was identified for potential groundwater contamination by relevant metabolites.

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 and groundwater, when surface water or groundwater are 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).

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

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No 283/2013, 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, EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

It is noted that some ecotoxicity studies were performed with the formulation ‘CHA 2745’ and not with the representative formulation ‘CHA 2745-02’. ‘CHA 2745’ contains coformulants which are not present in the representative formulation ‘CHA 2745-02’ and present an environmental classification. Overall, in the light of the available information, the use of toxicity endpoints from both formulations was considered as acceptable.

A low acute and chronic risk to birds and low acute risk to wild mammals was concluded for pethoxamid for all exposure routes and for all representative uses. The long-term risk to wild mammals for pethoxamid was discussed at the Pesticides Peer Review experts’ meeting 160 (14–16 June 2017). By using the agreed ecotoxicologically relevant endpoint, the refined DT\(_{50}\) for grass and weeds and the information provided indicating that small herbivorous mammals are not expected to be in the maize field at the earlier growth stages (BBCH 10–29) of maize, a low long-term risk for wild mammals was concluded. The risk to birds and mammals for the plant metabolites of pethoxamid MET-30, MET-42 and MET-47 was considered as covered by the risk assessment of the parent. A low risk via secondary poisoning was concluded for the pertinent surface water metabolites (\(\log K_{ow} > 3\)), MET-6 and MET-22.

A low acute risk to aquatic organisms was concluded for pethoxamid for all representative uses (provided that mitigation measures are implemented; see Section 8) whilst a high chronic risk was concluded for various FOCUS scenarios. The available refinements to the aquatic risk assessment were discussed at the Pesticides Peer Review experts’ meeting 160 (14–16 June 2017). The proposed refinement based on the species sensitivity distribution (SSD) of macrophytes was considered as not acceptable since, after the assessment of the validity of the available studies, the data were not enough to build a SSD. In addition, the use of the geomean approach for the refinement of the chronic risk assessment was not supported in line with the agreements of the Pesticide Peer Review meeting 133. The experts agreed to use in the refined risk assessment the (Ecological Threshold Option-Regulatory Acceptable Concentration) ETO-RAC derived from the available mesocosm study with an assessment factor of 3. By using this refinement in the risk assessment, a high risk was still identified for the FOCUS scenario R4 (data gap).

Ecotoxicological data for the pertinent surface water metabolites were available for the most sensitive taxonomic group (algae) with the exception of MET-101, MET-46, MET-102 and MET-30. QSAR
estimates were available and were considered acceptable only for MET-46 and MET-102; while there are uncertainties associated with such predictions, in this specific case, the in silico predictions were supported by the close structural similarity between these metabolites and MET-22 for which laboratory toxicity data were available. Considering that the toxophore appeared to be lost for all metabolites, the Regulatory Acceptable Concentration (RAC) of the parent compound was used for all the taxonomic groups for which ecotoxicological data were not available. By performing the risk assessment in line with the above considerations, a high chronic risk to fish could not be excluded for MET-42, MET-101 and MET-100 (data gap). A high risk to algae and aquatic plants could not be excluded for MET-101 and MET-30, and a high risk to aquatic plants could not be excluded for MET-102 (data gap). A low risk was concluded for all the remaining taxonomic groups and surface water metabolites.

Suitable acute (oral and contact) and chronic toxicity studies on honey bees were available for the active substance and the representative formulation. In addition, a repeated exposure toxicity study with honeybee larvae (8 days) was available. No information was submitted regarding potential sublethal effects, e.g. on the hypopharyngeal gland (HPG) (data gap). A risk assessment was performed by the RMS according to EFSA (2013). A low acute risk, via contact and oral exposure, and a low chronic risk to larvae was concluded for all the representative uses while a high chronic risk was not excluded for adult honeybees, at the screening level assessment. At Tier 1 level, a low chronic risk was concluded for all uses and scenarios, with the exception of the flowering weeds scenario for which a high risk was identified. The latter scenario, however, can be considered of low relevance for this substance and the representative uses. A low acute and chronic (adult and larvae) risk to honeybees via exposure to surface and puddle water was concluded for all the representative uses. A high chronic (adult and larvae) risk to honeybees could not be excluded for exposure via guttation water (data gap) while a low acute risk was concluded. A suitable assessment for accumulative effects was not available. The available information was not sufficient to address the risk from metabolites occurring in pollen and nectar (data gap). The RMS disagreed with this data gap.

Acute oral and contact toxicity data were available for bumblebees (Bombus terrestris) while for solitary bees (Osmia bicornis) only contact toxicity data were available. By using these data in the risk assessment, a low acute risk was concluded for solitary bees while for bumblebees a low risk was concluded for all scenarios with the exception of the flowering weeds scenario for which a high risk was identified. The latter scenario, however, can be considered of low relevance for this substance and the representative uses. A low acute and chronic (adult and larvae) risk to honeybees via exposure to surface and puddle water was concluded for all the representative uses. A high chronic (adult and larvae) risk to honeybees could not be excluded for exposure via guttation water (data gap) while a low acute risk was concluded. A suitable assessment for accumulative effects was not available. The available information was not sufficient to address the risk from metabolites occurring in pollen and nectar (data gap). The RMS disagreed with this data gap.

A low risk to non-target arthropods for pethoxamid was concluded.

The risk assessment for earthworms was discussed at the Pesticides Peer Review experts’ meeting 160 (14–16 June 2017). The studies available in the dossier were not performed in line with the data requirements. Two additional studies were submitted performed with a product containing pethoxamid and an additional active substance (clomazone or picloram) where the test item was incorporated into the soil, in line with the data requirements. Considering this additional information, the overall data package for earthworms was considered by the experts as sufficient for the risk assessment. By using these data in a risk assessment, a high risk to earthworms for pethoxamid was concluded. The available high tier refinements (field studies) were discussed by the experts. The experts agreed to use the available field study performed in line with the representative pre-emergence use on maize (worst case). Considering this study, a low risk to earthworms for pethoxamid was concluded. It is noted that the representativeness of this study at Member State level might need to be further checked. A low risk to soil meso- and macrofauna (predatory mites and Collembola) was concluded for pethoxamid.

A low risk to soil meso- and macrofauna (including earthworms) was concluded for all the pertinent soil metabolites with the exception of MET-101 for which a high risk could not be excluded for earthworms when 10 times higher toxicity than the parent compound is assumed (data gap). It needs to be noted that this metabolite has not been tested due to issues with its synthesis.

A low risk to soil microorganisms was concluded for pethoxamid and all the pertinent soil metabolites.

A low risk to non-target terrestrial plants and biological methods of sewage treatment for pethoxamid was concluded.

The ecotoxicity data available for pethoxamid are not sufficient to conclude on the endocrine disrupting potential of pethoxamid in non-target organisms. Pending on the outcome of the data gap in Section 2, further ecotoxicological tests might be necessary to address the potential endocrine disrupting properties of pethoxamid.
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 |
|-----------------------------|-------------|---------------|
| Pethoxamid                  | Low (DT<sub>50</sub> = 5.5–8.1 days) | Low risk |
| MET-42                      | Moderate to medium (DT<sub>50</sub> = 31.5–82.0 days) | Low risk |
| MET-100                     | Low to medium (DT<sub>50</sub> = 9.1–85.5 days) | Low risk |
| MET-101                     | Moderate to high (DT<sub>50</sub> = 27.3–106 days) | Data gap |
| MET-22 (formed under anaerobic conditions not expected for the representative uses on maize and soya) | Moderate to medium (DT<sub>50</sub> = 15.6–96.2 days) | Low risk |
| MET-46 (formed under anaerobic conditions not expected for the representative uses on maize and soya) | Very low (DT<sub>50</sub> = 0.2–0.4 days) | Low risk |

DT<sub>50</sub>: period required for 50% dissipation.

Table 2: Groundwater

| Compound (name and/or code) | Mobility in soil | > 0.1 µg/L at 1 m depth for the representative uses<sup>(a)</sup> | Pesticidal activity | Toxicological relevance |
|-----------------------------|------------------|-------------------------------------------------------------|---------------------|-------------------------|
| Pethoxamid                  | High to medium (<i>K<sub>DOC</sub> = 187–241 mL/g</i>) | FOCUS GW: no                                               | Yes                 | Yes                     |
| MET-42                      | Very high (<i>K<sub>DOC</sub> = 5–10 mL/g</i>)       | FOCUS GW: yes, 8/8 scenarios, 7/8 > 0.75 µg/L and 3/8 > 10 µg/L | No                  | Yes, due to the proposed classification Carc cat 2 for pethoxamid |
| MET-100                     | Very high (<i>K<sub>DOC</sub> = 1–4 mL/g</i>)       | FOCUS GW: yes, 8/8 scenarios, 7/8 > 0.75 µg/L               | No                  | Yes, due to the proposed classification Carc cat 2 for pethoxamid |
| Compound (name and/or code) | Mobility in soil | > 0.1 µg/L at 1 m depth for the representative uses<sup>(a)</sup> | Pesticidal activity | Toxicological relevance |
| MET-101                     | No data (<i>K<sub>DOC</sub> = 12.3 estimated from EPI Suite</i>) | FOCUS GW: yes, 8/8 scenarios, 7/8 > 0.75 µg/L and 3/8 > 10 µg/L | No                  | Yes, due to the proposed classification Carc cat 2 for pethoxamid |
| MET-22 (formed under anaerobic conditions not expected for the representative uses on maize and soya) | High (<i>K<sub>DOC</sub> = 88–129 mL/g</i>) | FOCUS GW: Yes, 5/8 scenarios                                | No                  | Yes, due to the proposed classification Carc cat 2 for pethoxamid |
### 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

| 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 |
|-----------------------------|------------------|------------------------------------------------------|---------------------|------------------------|
| MET-46 (formed under anaerobic conditions not expected for the representative uses on maize and soya) | No data (K<sub>DOC</sub> = 0 assumed for assessment) | FOCUS GW: No | No | Assessment not triggered, but would be relevant due to the proposed classification Carc cat 2 for pethoxamid |

K<sub>DOC</sub>: Freundlich organic carbon adsorption coefficient; K<sub>DOC</sub>: organic carbon linear adsorption coefficient; FOCUS GW: Forum for the Co-ordination of Pesticide Fate Models and their Use Ground Water. 

(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

| Compound (name and/or code) | Ecotoxicology |
|-----------------------------|---------------|
| Pethoxamid (water and sediment) | High risk for 1/8 FOCUS scenario |
| MET-42 (water and sediment) | Data gap |
| MET-100 (water and sediment) | Data gap |
| MET-101 (water and sediment) | Data gap |
| MET-22 (water and sediment) | Low risk |
| MET-46 (water and sediment) | Low risk |
| MET-102 (water and sediment) | Data gap |
| MET-30 (water and sediment) | Data gap |
| MET-104 (water and sediment) | Low risk |
| MET-6 (water and sediment) | Low risk |
| Benzoic acid (water and sediment) | Low risk |

FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use.

Table 4: Air

| Compound (name and/or code) | Toxicology |
|-----------------------------|------------|
| Pethoxamid | Rat LC<sub>50</sub> > 4.16 mg/L air per 4 h (whole body, maximum attainable concentration) |

LC<sub>50</sub>: 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).

- A monitoring method for the determination of all components included in the residue definition for monitoring purposes for groundwater (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 1).
- Further investigation of comparative *in vitro* metabolism (for animal species used in pivotal studies and human material, microsomes or intact cell systems) (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 2).
- Further investigation on whether adverse effects on the hypothalamic–pituitary–thyroid (HPT) axis (including thyroid tumours) should be considered as indication of endocrine disruption potential of pethoxamid (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 2).
- Toxicological data to define the toxicological profile of MET-30 in comparison to pethoxamid (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 2).
- Further toxicological data relevant to consumer risk assessment of groundwater metabolites MET-100 and MET-101, provided that the metabolites are demonstrated not to be relevant according to the guidance document on the assessment of the metabolites in groundwater or classification as Carc. Cat. 2 of the parent pethoxamid is not agreed under Regulation (EC) 1272/2008 (potentially relevant for all representative uses; submission date proposed by the applicant: unknown; see Sections 2, 3 and 4).
- Applicant to identify further metabolites that may be found in leafy and fruit crops that can be grown in rotation; MET-30 may need to be considered for the risk assessment of these crops and the consumer risk assessment cannot be concluded at this stage (relevant for all representative uses evaluated; submission date proposed by the applicant: no data available; see Section 3).
- Data on residue levels in pollen and bee products for human consumption (relevant for all representative uses evaluated; submission date proposed by the applicant: no data available; see Section 3).
- Applicant to provide information and/or data on possible transformation products of pethoxamid or its metabolites under conditions of water treatment (e.g. ozonation, chlorination). In particular, the information provided by the applicant during the peer review is insufficient to address transformation products resulting from chlorination treatment procedures (relevant for all representative uses evaluated; submission date proposed by the applicant: no date proposed; see Section 4).
- Further information to address the risk to aquatic organisms for pethoxamid for the FOCUS scenario R4 (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to aquatic organisms for MET-30, MET-42, MET-100, MET-101 and MET-102 (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to honeybees from pethoxamid via exposure to guttation water and the risk to honeybees from metabolites occurring in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information regarding potential sublethal effects on honeybees e.g. on the HPG (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to earthworms for MET-101 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
8. **Particular conditions proposed to be taken into account to manage the risk(s) identified**

- Operators should use personal protective equipment (i.e. gloves during mixing/loading, and gloves, a coverall and sturdy footwear during application) to reduce exposure below the AOEL (see Section 2).
- For all representative uses: mitigation measures up to 20 m no-spray buffer combined with vegetated buffer strip are needed to mitigate the acute and chronic risk to aquatic organisms for the FOCUS scenarios R1 and R2. Mitigation measures such as 5 m no-spray buffer zone are needed for the D3, D4, D5, D6 and R3 FOCUS scenarios (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 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) The need for further tests and risk assessment to unique human metabolites could not be finalised while an *in vitro* comparative metabolism study was not submitted (see Section 2).

2) Pethoxamid does not meet the interim criteria for endocrine disruption. Regarding the scientific risk assessment, further data are needed to conclude (see Section 2).

3) Consumer risk assessment cannot be concluded for the situations where leafy and fruity crops are planted as succeeding crops or in case of crop failure (see Section 3).

4) Consumer risk assessment cannot be finalised in relation to possible transformation products of pethoxamid or its metabolites under conditions of water treatment (e.g. ozonation, chlorination) (see Section 4).

9.2. **Critical areas of concern**

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at 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.

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.

5) Groundwater contamination by relevant metabolites MET-42, MET-100 and MET-101 above the parametric drinking water limit of 0.1 μg/L in the majority of scenarios even when the substance is applied every second year (see Sections 2 and 4).

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6 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.
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.)

All columns are grey as relevant metabolites MET-42, MET-100 and MET-101 are found in the groundwater above the parametric drinking water limit of 0.1 μg/L in the majority of scenarios even when the substance is applied every second year.

Table 5: Overview of concerns

| Representative use                          | Maize BBCH 0-9 | Maize BBCH 10-14 | Soya bean BBCH 0-9 |
|--------------------------------------------|----------------|------------------|-------------------|
| **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 |                  |
| Risk to wild non-target terrestrial vertebrates | Risk identified | Assessment not finalised |                  |
| Risk to wild non-target terrestrial organisms other than vertebrates | Risk identified | Assessment not finalised |                  |
| Risk to aquatic organisms                  | Risk identified | 1/8 FOCUS scenario | 1/8 FOCUS scenario | 1/8 FOCUS scenario |
| Groundwater exposure to active substance   | Legal parametric value breached | Assessment not finalised |                  |
| Groundwater exposure to metabolites        | Legal parametric value breached(a) | 10 μg/L(b) breached |                  |

|                                | X3,4 | X3,4 | X3,4 |
|--------------------------------|------|------|------|

BBCH: growth stages of mono- and dicotyledonous plants. 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): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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### Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| a.s.         | active substance |
| AAOEL        | acute acceptable operator exposure level |
| ADI          | acceptable daily intake |
| AOEL         | acceptable operator exposure level |
| AR           | applied radioactivity |
| ARFD         | acute reference dose |
| BBCH         | growth stages of mono- and dicotyledonous plants |
| bw           | body weight |
| CAR          | constitutive androstane receptor |
| DT$_{50}$    | period required for 50% dissipation (define method of estimation) |
| EC           | emulsion concentrate |
| ECHA         | European Chemicals Agency |
| ETO-RAC      | Ecological Threshold Option- Regulatory Acceptable Concentration |
| EUROPOEM     | European Predictive Operator Exposure Model |
| FAO          | Food and Agriculture Organization of the United Nations |
| FOCUS        | Forum for the Co-ordination of Pesticide Fate Models and their Use |
| GAP          | Good Agricultural Practice |
| HPG          | hypopharyngeal glands |
| HPT          | hypothalamic-pituitary-thyroid axis |
| 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) |
| $K_{doc}$    | organic carbon linear adsorption coefficient |
| $K_{Foc}$    | Freundlich organic carbon adsorption coefficient |
| $K_{ow}$     | octanol/water partition coefficient |
| LC$_{50}$    | lethal concentration, median |
| LC-MS/MS     | liquid chromatography with tandem mass spectrometry |
| LOAEL        | lowest observable adverse effect level |
| LOQ          | limit of quantification |
| MRL          | maximum residue level |
| mRNA         | Messenger ribonucleic acid |
| NOAEL        | no observed adverse effect level |
| OECD         | Organisation for Economic Co-operation and Development |
| PEC          | predicted environmental concentration |
| PEC$_{sed}$  | predicted environmental concentration in sediment |
| PEC$_{sw}$   | predicted environmental concentration in surface water |
| $P_{ow}$     | partition coefficient between n-octanol and water |
| PPE          | personal protective equipment |
| QSAR         | quantitative structure-activity relationship |
| QuEChERS     | quick, easy, cheap, effective and safe method |
| RAC          | Regulatory Acceptable Concentration |
| RAR          | Renewal Assessment Report |
| RMS          | rapporteur Member State |
| SMILES       | simplified molecular-input line-entry system |
| SSD          | species sensitivity distribution |
| UDP          | uridine diphosphate |
| UGT          | UDP-glucuronosyltransferase |
| UF           | uncertainty factor |
| WHO          | World Health Organization |
Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2017.4981
## Appendix B – Used compound codes

| Code/trivial name | Chemical name/SMILES notation                                                                                                                                                                                                 | Structural formula |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| MET-42           | 2-[(2-ethoxyethyl)(2-methyl-1-phenylprop-1-en-1-yl)amino]-2-oxoethanesulfonic acid  
O=S(=O)(O)CC(=O)N(COCC)C(=C(\(\text{C\})\text{C})c1ccc1)                                                                                                               | ![MET-42 structural formula](image1) |
| MET-100          | N-(2-methyl-1-phenylprop-1-en-1-yl)-N-(sulfoacetyl)glycine  
O=S(=O)(O)CC(=O)N(CC(=O)O)(C(=C(\(\text{C}\))\text{C})c1ccc1)                                                                                                                | ![MET-100 structural formula](image2) |
| MET-101          | N-(2-ethoxyethyl)-N-[(1Z)-3-hydroxy-2-methyl-1-phenylprop-1-en-1-yl]-2-mercaptoacetamide  
SCC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                                                  | ![MET-101 structural formula](image3) |
| MET-22           | N-(2-ethoxyethyl)-N-(2-methyl-1-phenylprop-1-en-1-yl)acetamide  
CC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                                               | ![MET-22 structural formula](image4) |
| MET-46           | N-[2-(2-hydroxyethoxy)ethyl]-N-(2-methyl-1-phenylprop-1-en-1-yl)acetamide  
CC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                                               | ![MET-46 structural formula](image5) |
| MET-102          | N-(2-ethoxyethyl)-N-[(1Z)-3-hydroxy-2-methyl-1-phenylprop-1-en-1-yl]acetamide  
CC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                                               | ![MET-102 structural formula](image6) |
| MET-30           | S-2-[(2-ethoxyethyl)(2-methyl-1-phenylprop-1-en-1-yl)amino]-2-oxoethyl-\text{-D,L-cysteine}  
O=C(O)CCSCC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                              | ![MET-30 structural formula](image7) |
| MET-104          | 2-[(2-ethoxyethyl)(2-methyl-1-phenylprop-1-en-1-yl)amino]-2-oxoethyl thiocyanate  
N#SCC(=O)N(COCC)C(=C(\(\text{C}\))\text{C})c1ccc1                                                                                                 | ![MET-104 structural formula](image8) |
| Code/trivial name | Chemical name/SMILES notation | Structural formula |
|-------------------|-------------------------------|--------------------|
| MET-6             | \(N\)-(2-ethoxyethyl)-\(N\)-(2-methyl-1-phenylprop-1-en-1-yl)-2-(methylthio)acetamide\) | ![MET-6 Structural formula](image) |
|                   | \(\text{CSCC}(-\text{O})\text{N}((\text{CCOCC})\text{C}(-\text{C}(-\text{C}))\text{C}1\text{ccc}1)\) | |
| **Benzoic acid**  | Benzoic acid                  | ![Benzoic acid Structural formula](image) |
|                   | \(\text{O=C(O)c1ccc1}\)      | |
| MET-47            | \(N\)-(carboxyacetyl)-\(S\)-\{2-[(2-ethoxyethyl)(2-methyl-1-phenylprop-1-en-1-yl)amino]-2-oxoethyl\}-\(\text{D,L-cysteine}\) | ![MET-47 Structural formula](image) |
|                   | \(\text{O=C(O)c1ccc1})\text{C}((\text{C})\text{C})(-\text{O})\text{O}\) | |

SMILES: simplified molecular-input line-entry system.