CONCLUSION ON PESTICIDES PEER REVIEW

EFSA Journal

APPROVED: 20 December 2017

doi: 10.2903/j.efsa.2018.5151

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Finland, and co-rapporteur Member State, Denmark, for the pesticide active substance phenmedipham 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 phenmedipham as a herbicide on sugar beet/fodder beet. The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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

Requestor: European Commission

Question number: EFSA-Q-2015-00111

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Suggested citation: EFSA (European Food Safety Authority), Arena M, Auteri D, Barmaz S, Bellisai G, Brancato A, Brocca D, Bura L, Byers H, Chiusolo A, Court Marques D, Crivellente F, De Lentdecker C, Egsmose M, Erdos Z, Fait G, Ferreira L, Goumenou M, Greco L, IppolitoA, Istace F, Jarrah S, Kardassi D, Leuschner R, Lythgo C, Magrans JO, Medina P, Miron I, Molnar T, Nougadere A, Padovani L, Parra Morte JM, Pedersen R, Reich H, SacchiA, Santos M, Serafimova R, Sharp R, Stanek A, Streissl F, Sturma J, Szentes C, Tarazona J, Terron A, Theobald A, Vagenende B, Verani A and Villamar-Bouza L, 2018. Conclusion on the peer review of the pesticide risk assessment of the active substance phenmedipham. EFSA Journal 2018;16(1):5151, 25 pp. https://doi.org/10.2903/j.efsa.2018.5151

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

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. Phenmedipham is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Finland, and co-rapporteur Member State (co-RMS), Denmark, received an application from the Task Force on Phenmedipham, comprising UPL Europe Ltd and Bayer CropScience AG, for the renewal of approval of the active substance phenmedipham. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Denmark), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on phenmedipham in the renewal assessment report (RAR), which was received by EFSA on 21 December 2016. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants of the Task Force on Phenmedipham, for comments on 20 February 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 27 April 2017.

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 expert 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 phenmedipham 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 phenmedipham as a post-emergence herbicide on sugar beet/fodder beet as proposed by the applicants. Full details of the representative uses can be found in Appendix A of this report.

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

A data gap was identified for a search of the scientific peer-reviewed open literature on the active substance and its metabolites relevant to consumer exposure.

In the area of identity, physical/chemical properties and analytical methods data gaps were identified for spectra of the relevant impurities, for the content of the relevant impurities before and after storage and for a method for determination of the relevant impurities in the representative formulation.

In the mammalian toxicology area, data gaps were identified in relation to toxicokinetics, skin sensitisation, possible phototoxicity within ultraviolet B (UVB) wavelength, the need for genotoxicity and/or repeat-dose toxicity data on the plant and livestock metabolites and data to address the toxicological relevance of most impurities present in the technical specifications. In addition, information on analytical methods used in the toxicological studies as well as acute toxicity studies on the representative plant protection product or equivalent formulation are missing. The reproductive toxicity and genotoxicity potential of phenmedipham have not been adequately addressed; regarding genotoxicity, no adequate *in vivo* follow-up to the positive clastogenic effects observed *in vitro* has been provided; therefore, a genotoxic concern cannot be ruled out. Phenmedipham is proposed to be classified by the peer review (but not according to the harmonised classification) as a carcinogen and reproductive toxicant category 2; 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 (ED) properties are met. In addition, an ED mode of action could not be ruled out considering the adverse effects observed in pituitary, uterus, prostate, testis and adrenals supported by ToxCast data, and therefore, a critical area of concern is identified. Other critical areas of concern are identified as the technical specifications proposed are not covered by the batches used in key toxicological studies; toxicological reference values cannot be established as the genotoxicity potential of phenmedipham is not clarified, and consequently, the non-dietary exposure assessment could not be finalised.

In the residue section, several data gaps were identified related to the representative uses with regard to processed commodities, residue trials including a comprehensive livestock assessment. A consumer risk assessment could not be conducted in the absence of toxicological reference values.

With respect to the fate and behaviour in the environment, the necessary information was available to conduct the exposure assessment for groundwater and the environment. 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 is abstracted for drinking water. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised.

A number of data gaps were identified in the field of ecotoxicology in relation to dietary risk to mammals, the risk to the algae and aquatic invertebrates and the risk to bees. The risk assessment to mammals and aquatic organisms (algae) could not be finalised.

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Background

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

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

In accordance with Article 1 of the Regulation, the RMS, Finland, and co-RMS, Denmark, received an application from the Task Force on Phenmedipham, comprising of UPL Europe Ltd and Bayer CropScience AG, for the renewal of approval of the active substance phenmedipham. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Denmark), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on phenmedipham in the RAR, which was received by EFSA on 21 December 2016 (Finland, 2016).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants of the Task Force on Phenmedipham, for consultation and comments on 20 February 2017. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 27 April 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 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 expert 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, the RMS and co-RMS on 20 June 2017. 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 expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology.

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

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 December 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 phenmedipham as a post-emergence herbicide on sugar beet/fodder beet, as proposed by 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.

applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 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 (26 June 2017);
- the evaluation table (19 December 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 (Finland, 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

Phenmedipham is the ISO common name for methyl 3-(3-methylcarbaniloyloxy)carbanilate or 3-methoxycarbonylaminophenyl 3-methylcarbanilate (IUPAC).

The representative formulated product for the evaluation was 'PMP SE160', a suspo-emulsion (SE) containing 160 g/L phenmedipham.

The representative uses evaluated were broadcast spray applications in the post-emergence stage of beets (sugar and fodder), to control broad-leaved weeds and grasses. 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 phenmedipham according to the representative uses proposed at the EU level result in a sufficient herbicidal efficacy against the target weeds, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014).

A data gap has been identified for a search of the scientific peer-reviewed open literature on the active substance and its metabolites relevant to consumer exposure, dealing with side effects on health, and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011).

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 specifications were supported by batch data from industrial scale productions and quality control (QC) data. The proposed minimum purity of the technical material is 970 g/kg. Toluene with maximum content of 2 g/kg, 3-methylaniline and 3-aminophenol with a maximum content of 1 g/kg each are considered relevant impurities. It should be noted that the relevance of other impurities is not concluded (see Section 2). The manufactured technical material meets the requirements of the existing FAO specification (AGP: CP/90, 1980) in terms of minimum purity; relevant impurities are not mentioned in the FAO specification.

The batches used in the (eco) toxicological assessment do not support the proposed new specification (for both sources) neither the original reference specification (from Bayer). This constitutes a critical area of concern for Sections 2 and 5.

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 phenmedipham or the representative formulation; however, data gaps were identified for spectra of the relevant impurities and for the content of the relevant impurities before and after storage. The main data regarding the identity of phenmedipham and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of preapproval data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation and for the determination of the respective impurities in the technical material. However, a data gap was identified for a validated method for determination of the relevant impurities in the representative formulation.

Phenmedipham residue can be monitored in food and feed of plant origin by the multiresidue method DFG S19 (extended revision) 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. In addition, there is Quick Easy Cheap Effective Rugged Safe (QuEChERS) method using gas chromatography-mass spectrometry (GC-MS) and/or LC-MS/MS for all plant commodities with LOQs in the range 0.01–0.05 mg/kg. It should be noted that a residue definition for monitoring in plant processed commodities is proposed. In case a specific maximum residue level (MRL) for these commodities is set, monitoring methods for the components included in the residue definition might be required. Residues of MHPC in food of animal origin can be determined by QuEChERS method using LC-MS/MS with LOQ of 0.01 mg/kg in all animal matrices.

Residues of phenmedipham and MHPC in soil can be monitored by DFG method S19 (extended revision) with LC-MS/MS with a LOQ 0.01 mg/kg.

Appropriate LC-MS/MS method exists for monitoring of phenmedipham and MHPC residues in water with a LOQ of 0.05 μg/L. Phenmedipham residues in air can be monitored by reversed phase high performance liquid chromatography with UV detector (RP/HPLC-UV) with a LOQ of 10 $\mu g/m^3$.

LC-MS/MS method with a LOQ of 50 μg/L can be used for monitoring of phenmedipham and MHPC in body fluids. The method for monitoring in animal products can be used for determination of phenmedipham and MHPC in body tissues.

2. Mammalian toxicity

The toxicological profile of the active substance phenmedipham was discussed at the Pesticides Peer Review Experts' Meeting 168 (October 2017) and assessed based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003), SANCO/10597/2003-rev. 10.1 (European Commission, 2012), Guidance on dermal absorption (EFSA PPR Panel, 2012) and Guidance on the application of the classification, labelling and packaging (CLP) Criteria (ECHA, 2015).

The technical specifications proposed by both applicants, including the original one from Bayer, are not supported by the toxicological assessment, leading to a critical area of concern. In addition, the assessment of the toxicological relevance of most impurities has not been addressed (data gap). Toluene, 3-aminophenol and 3-methylaniline are relevant impurities due to their hazard, but their maximum levels proposed for the technical specifications (2 g/kg, 1 g/kg and 1 g/kg, respectively) are not of toxicological concern. Analytical methods for rodent diet have been provided in the respective section of the RAR; it has to be further clarified which method has been used in each of the toxicological studies (data gap).

Phenmedipham absorption is relatively fast and extensive in the low doses (about 80% in 24 h). Phenmedipham is widely distributed with higher amounts in plasma, whole blood, lungs, ovaries, thyroid gland, skin, pituitary, heart, adrenal glands, kidneys, spleen and liver. Around 90% of phenmedipham is excreted within 24 h through the urine after low-dose administration, while at high doses, the elimination is less fast and mainly through faeces. Basic toxicokinetic data have not been investigated in rodents and a data gap was identified. Phenmedipham is extensively metabolised in the rat via oxidative/hydrolytic cleavage followed by hydroxylation, acetylation and oxidation reactions. The major component in faeces is the parent compound. In the comparative interspecies (rat and human), metabolism study *in vitro* significant differences and human specific metabolites were not observed. Since the metabolite MHPC has been identified as a major metabolite in rats, it should be included in the residue definition for monitoring in body fluids (blood, plasma and urine) in humans together with the parent phenmedipham.

Low acute toxicity was observed when phenmedipham was administered by the oral, dermal or inhalation routes; no skin or eye irritation was attributed to the active substance. A conclusion regarding the potential for phenmedipham to cause skin sensitisation cannot be drawn due to insufficient data (data gap). Phenmedipham did not show phototoxic potential in the OECD 3T3 NRU-PT test. The OECD 3T3 NRU-PT test might not be an appropriate test for UVB absorbers such as phenmedipham. However, no validated methods are available to address properly UVB absorbers (data gap).

In all short-term studies in rats, mice and dogs, the critical effects observed were related to haemolytic anaemia (increased methaemoglobin (MetHB), decrease in haemoglobin, haematocrit and red blood cells, increased extramedullary haematopoiesis and haemosiderin deposition in spleen, liver and kidneys). The overall short-term no-observed adverse effect level (NOAEL) is 3.5 mg/kg body weight (bw) per day from the 90-day rat studies. Phenmedipham is clastogenic *in vitro* as demonstrated by the positive *in vitro* chromosomal aberration (CA) assays in human lymphocytes and in Chinese hamster ovary (CHO) cells. In the follow-up, *in vivo* mouse micronucleus (MN) assay provided the bone marrow was not sufficiently exposed and a conclusion in relation to the genotoxicity potential of phenmedipham cannot be drawn (data gap) since positive effects were observed *in vitro*, a genotoxic potential for phenmedipham cannot be excluded and this represents a critical area of concern.

The relevant long-term NOAEL is 3 mg/kg bw per day from a 2-year study in rats, based on haemolytic anaemia (haemosiderin deposition in spleen and liver) as well as histopathological effects in pituitary and kidney. An increased incidence of endometrial stromal sarcoma and of pituitary adenoma was observed in the 2-year studies in rats. On this basis, the peer review considered that classification as carcinogen Category 2[3] (Carc. 2, H351) may be appropriate for phenmedipham according to the criteria of Regulation (EC) 1272/2008.[4] The mechanism of carcinogenicity was not investigated and a genotoxic potential for phenmedipham is not excluded.

Two main and one supplementary multigenerational reproductive studies in rats were submitted for phenmedipham. The parental NOAEL is set at 22 mg/kg bw per day based on reduced maternal body weight gain during the premating period. The NOAEL for offspring is set at 25 mg/kg bw per day based on decreased body weight gain in F0 and more pronounced in F1 pups during lactation. In relation to the reproduction, information related to the most sensitive end points (such as sperm-related endpoints which were affected by the structural analogue desmedipham) is missing and a NOAEL cannot be set (data gap). Three acceptable developmental studies were provided (one in rat and two in rabbits). For both maternal and developmental toxicity in rats, a lowest observable adverse effect level (LOAEL) is set at the low dose of 150 mg/kg bw per day based on reduced body weight gain in dams and occurrence of runts in all doses. For rabbits, a maternal NOAEL is set at 225 mg/kg bw per day based on reduced body weight gain and reduced food consumption. The developmental NOAEL was also set at 225 mg/kg bw per day based on reduced body weight and retarded ossification. Based on the high incidence of runts in rats in all treatment groups, the peer review considered that classification of phenmedipham for developmental toxicity category 2 may be appropriate according to the criteria of Regulation (EC) 1272/2008. Overall, the available data for phenmedipham do not raise concern in relation to neurotoxicity or immunotoxicity.

Phenmedipham is listed in Annex VI of Regulation (EC) 1272/2008 and no classification for human health is included. The developmental toxicity studies were available in the original dossier, but EFSA does not have information regarding the assessment of carcinogenicity and developmental toxicity by the European Chemicals Bureau (ECB) regarding the consideration of the substance under the previous regulatory frame for classification and labelling. Following the present re-evaluation, the peer review proposed a classification as carcinogen Category 2 (a new related study was submitted) and as developmental toxicity Category 2 (for developmental effects observed in previously evaluated studies). Based on this proposal, the conditions of the interim provisions of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting (ED) properties are met, leading to a critical area of concern. In addition, an ED-mediated mode of action for the effects observed in the pituitary, uterus, prostate, testis and adrenals, supported by ToxCast data could not be ruled out, and further mechanistic clarifications are needed such as level 2

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

[4] 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, 1–1355.

and 3 of the OECD conceptual framework (OECD, 2012), analysed according to the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA Scientific Committee, 2013) (data gap). During the first peer review of phenmedipham (European Commission, 2004), an acceptable daily intake (ADI) of 0.03 mg/kg bw per day was derived, on the basis of the 2-year rat study and applying an uncertainty factor of 100. An acute reference dose (ARfD) was not allocated, and an acceptable operator exposure level (AOEL) of 0.13 mg/kg bw per day was established on the basis of the 90-day rat study (uncertainty factor (UF) 100, no correction for oral absorption). The reference values (under the renewal process) were discussed by the experts; however, they cannot be established as long as the mutagenic potential of phenmedipham cannot be excluded (critical area of concern).

Acute toxicity studies were not submitted with the representative plant protection product (PPP) or equivalent formulation; some endpoints regarding the acute toxicity were determined by the use of calculation rules and also a local lymph node assay (LLNA) study was submitted; however, the toxicity of the plant protection product and its relation to the toxicity of the active substance, adverse effects and relative hazard associated with the different routes of exposure cannot be fully drawn (data gap). The dermal absorption values based on an *in vitro* human study using the representative formulation for phenmedipham are 0.2% for the neat formulation (160 g/L), 1% for the spray dilution (2 g/L) and 2.5% for *pro-rata* correction (0.8 g/L). Considering the lack of reference values, the operator, worker, bystander and resident risk assessment could not be conducted (issue that could not be finalised).

A number of metabolites were found in significant amounts in residues. MHPC has been identified as a major metabolite in the rat and the reference values of phenmedipham, or the lack of them, are applicable to this metabolite. For 3-methylaniline (*m*-toluidine), which has harmonised classification as Acute tox 3, H301, H311, H331: toxic if swallowed, if inhaled and in contact with skin, and STOT-RE 2, H373: may cause damage to organs through prolonged or repeated exposure, genotoxicity and repeated-dose toxicity data relevant to consumer exposure are needed. Regarding metabolites 3-aminophenol, 3-acetamidophenol, 4-acetamido-*o*-cresol, 4-aminocresol, acetamido-benzoic acid, aminobenzoic acid and *m*-acetotoluidine, their genotoxic potential has to be addressed, and pending on further assessment in the residue section, repeated-dose toxicity data relevant to consumer exposure may be needed (data gap).

3. Residues

The assessment in the residue section is based on the OECD guidance document on overview of the residue chemistry studies (OECD, 2009), the OECD publication on the MRL calculations (OECD, 2011) and the European Commission guideline document on the MRL setting (European Commission, 2011).

Phenmedipham was discussed at the Pesticides Peer Review Experts' Meeting 167 (October 2017).

Metabolism of phenmedipham in primary crops was investigated upon foliar application in roots/tuber crops (sugar beet) with both [amino-phenyl-UL-^{14}C] and [phenyl-methyl-UL-^{14}C] phenmedipham at max. 1,066 g/ha application rate, and in fruits (strawberries) only with [amino-phenyl-UL-^{14}C] radiolabelled phenmedipham at max. 2,880 g/ha application rate.

Phenmedipham and its conjugates were the predominant compounds of the total residues in sugar beet in immature and mature leaves (95% total radioactive residue (TRR) and 51% TRR, respectively). In sugar beet root, phenmedipham and its conjugates were detected at a low level (6.6% TRR) while a major unknown fraction accounted for ca. 26% TRR in roots and 14% TRR in maturity leaves. This fraction was generated only from the amino phenol moiety and constituted of several polar minor metabolite fractions. The metabolism data in sugar beet were considered sufficient to support the representative uses on sugar beet, except one MS who considered that a new metabolism study in root crops should be provided in view of the authorised uses on other root crops. In strawberries, phenmedipham was the main compound recovered in fruits (58% TRR) while 3-acetamidophenol compound accounted for 13% TRR. 3-acetamidophenol is a rat metabolite and it was not recovered in the sugar beet metabolism study. Based on these metabolism studies, the residue definition for monitoring was derived as phenmedipham restricted to roots and fruit crops only. For risk assessment residue definition, the experts were of the opinion, that in addition to phenmedipham also, glucoside conjugates should be included and the residue definition should be restricted to sugar beet only. For strawberries, since only one label was investigated, no residue definition for risk assessment was proposed. It should be noted that currently the genotoxic potential of phenmedipham cannot be

concluded (see data gap in Section 2). Provisional conversion factors (CFs) for risk assessment in sugar beet of 1.4 (root) and 1.2 (leaves) were derived from the metabolism studies.

Under standard hydrolysis conditions when investigated with phenyl-methyl labelling, phenmedipham degraded partially into 3-methylaniline (*m*-toluidine) at baking/brewing and boiling (86% applied radioactivity (AR)) and completely into 3-methylaniline (*m*-toluidine) under sterilisation conditions. Under these harsh conditions, it can reasonably be assumed that the formation of aniline can be excluded. For the amino phenol labelling form, a complete degradation of phenmedipham to MHPC metabolite was observed at baking/brewing and boiling and also in conditions representative of sugar production. Under pasteurisation conditions, phenmedipham is considered stable for both labelling forms (82–87% of AR). The residue definitions for monitoring in processed commodities is sum of phenmedipham and MHPC, expressed as phenmedipham, while for risk assessment is separately 3-methylaniline (*m*-toluidine) (see data gap in Section 2) and sum of phenmedipham and MHPC. The possible formation of MHPC and 3-methylaniline (*m*-toluidine) in sugar and sugar beets by-products, used as feed item for animals, has to be also investigated (data gap).

A confined rotational crop study was conducted on wheat, turnip and chard with phenyl-methyl-UL-^{14}C phenmedipham at 30, 164 and 305 plant back intervals (PBIs). Although some deficiency was noted (low rate of identification), the metabolism pattern was considered sufficient because of the expected low residue levels in all edible parts. A second study was conducted with the amino-phenyl-UL-^{14}C phenmedipham form on lettuce, sugar beet and wheat at 30, 120 and 365 PBIs. The metabolic pattern was consistent throughout all PBIs with phenmedipham and MHPC (major soil metabolite) being the only identified metabolite in rotational crops. In wheat straw, phenmedipham (20% TRR) and MHPC (25% TRR) were the major compounds of the TRR (0.95 mg/kg). The same metabolic pattern was observed in cereal forage. A significant decline of the total residues from the first to the third rotation interval was observed. This is confirmed by the field rotational crop trials conducted on leafy (lettuce), root crops (carrots and turnip) and cereals (wheat and barley) showing that no residues of phenmedipham and MHPC are above 0.01 mg/kg. Based on the confined rotational studies, the risk assessment residue definition is proposed as sum of phenmedipham and MHPC, free and conjugates, expressed as phenmedipham, while for monitoring, the residue definition is set as phenmedipham only. For cereal fodder commodities, an average CF of 1.7 (1.3 for forage and 2.1 for straw) was derived based on the rotational metabolism studies while for sugar beet, the same CFs as for primary crops are applicable. However, these conversion factors should be regarded as provisional and have to be confirmed by the field residue trials.

Storage stability data demonstrated that phenmedipham and MHPC residues are stable up to 24 months in high water-, high oil-, high protein-, high starch- and high acid-content commodities, when stored at −20°C.

The submitted residue trials from southern Europe (SEU) are not valid since they were not compliant with the representative GAP. For northern Europe (NEU), three fully compliant and one slightly overdosed residue trials analysed according to the risk assessment residue definition were submitted for sugar beet roots, while for the leaves, only phenmedipham was investigated. Since a no-residue situation (lower than 0.01 mg/kg) cannot be confirmed, and no valid residue trials are available for SEU, sufficient number of residue trials compliant with the representative GAPs should be submitted (data gap).

Livestock metabolism studies were investigated with both methyl phenyl and amino labels in lactating goats for 3 days with a dose rate of 0.1 mg/kg bw per day. Although the dosing period and the storage of the samples for 8 months (milk) and 7 months (other tissues) are not compliant with the current recommendations, the studies were found acceptable to elucidate the metabolic pattern. Phenmedipham was extensively metabolised in ruminants resulting in a high number of compounds. The major compound were MHPC up to 38% TRRs in milk, 45% TRRs in kidney and 34% TRRs in liver, 3-aminophenol (16% TRRs) in kidney and (37% TRRs) in liver, 3-acetamidophenol in milk (23% TRRs) and (15% TRRs) in kidney, 4-acetamido-*o*-cresol (47% TRRs), 22% TRRs in milk, 4-aminocresol (24% TRRs) in kidney and (28% TRRs) in liver. In addition, acetamido-benzoic acid, aminobenzoic acid and *m*-acetotoluidine were also present for more than 10% of TRRs in liver. In muscle and fat, no metabolites identification was possible due to the very low TRRs recovered in these matrices (< 0.01 mg/kg). Preliminarily, taking into account the information available regarding the occurrence and toxicity of the recovered residue compounds, the residue definition for risk assessment for ruminants should include **MHPC, 3-aminophenol, 3-acetamidophenol, 4-acetamido-*o*-cresol, 4-aminocresol, acetamido-benzoic acid, aminobenzoic acid and *m*-acetotoluidine.** For monitoring, the residue definition is proposed as MHPC expressed as phenmedipham.

As regards the feeding studies, they were not submitted although based on the available data, they are triggered for all animal diets, except poultry (data gap). The feeding studies have to be covered by the storage stability data and validated analytical methods.

The livestock residue assessment should be regarded as provisional, pending on the finalisation of the assessment on processed commodities, the submission of the additional GAP compliant trials and the outcome of the toxicological evaluation of the components to be included in the residue definition (see Section 2).

Fish metabolism studies were not triggered.

The consumer risk assessment cannot be finalised in view of the various data gaps identified regarding the insufficient number of residue trials, the processing studies, the provisional livestock assessment, considering the toxicological profile of metabolites to be included in the risk assessment residue definition for animals (see Section 2) and provisional dietary burden calculations. Even an indicative consumer risk assessment cannot be conducted in the absence of toxicological reference values for phenmedipham.

Since during the peer review for the renewal of phenmedipham approval, different toxicological endpoints as well as residue definitions for risk assessment in plant and animal commodities were derived; the MRLs derived under Article 12 of the Regulation (EC) No 396/2005 should be revised (EFSA, 2014).

Considering that sugar beet and fodder beet are harvested before the flowering and provided that they are not cultivated for seed production, it can be reasonably assumed that bees will usually not get in contact with pollen, and therefore, the determination of residues in pollen and bee products is not considered necessary.

4. Environmental fate and behaviour

Phenmedipham was discussed at the Pesticides Peer Review Experts' Teleconference 151 (5 October 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, phenmedipham exhibited low to high persistence, forming the metabolite MHPC (max. 14% AR), which exhibited low to moderate persistence. Mineralisation of the ^{14}C methyl-aniline ring radiolabelled phenmedipham to carbon dioxide accounted for a maximum of 28.7% AR and the ^{14}C-amino-phenol labelled phenmedipham for a maximum of 20.2% AR after 112 days. The formation of unextractable residues for the ^{14}C-aniline ring and the ^{14}C-amino-phenol radiolabel accounted for maxima of 61.5% AR and 73.8% AR after 112 days, respectively. In the available anaerobic soil incubation, phenmedipham exhibited moderate persistence and produced the metabolite MHPC (max. 45.3% AR). Photolysis could marginally contribute to the degradation of phenmedipham in soil.

Field dissipation studies with phenmedipham were available in Germany and USA (California) in the first peer review. These studies have been considered not to provide reliable degradation half-lives during the renewal assessment.

Phenmedipham is expected to exhibit low mobility in soil and metabolite MHPC exhibited very high to high mobility on the basis of the available batch adsorption desorption studies.

In the available lysimeter studies (in the United Kingdom and Germany) of 2 or 3 years of duration, phenmedipham and MHPC were not found in the leachates at levels above 0.01 μg/L. Total radioactivity in the leachate amounted up to a maximum of 1.9 μg/L in the first year in the UK lysimeter study, attributed to humic acid type fragments and incorporated radioactivity in natural components.

At environmental relevant temperature, phenmedipham undergoes rapid aqueous hydrolysis under pH above 6 but slow or very slow hydrolysis at more acidic conditions. Photolysis in water is not expected to contribute to the degradation of phenmedipham in aquatic environment. In laboratory incubations in dark aerobic natural sediment water systems (pH 6.0–8.35), desmedipham exhibited very low persistence, forming the major metabolites MHPC (max. ca. 97.1% AR in whole system after one day, exhibiting low to medium persistence) and 3-methylaniline (*m*-toluidine) (max. 77% in whole system, very low to medium persistent). The unextractable sediment fraction was the major sink for the methyl-aniline and amino-phenol rings ^{14}C radiolabel moieties, accounting for up to maxima 73.4% AR and 78.0% AR, respectively, at the end of the study. Mineralisation accounted for 54.8% AR and 34.1% AR for the methyl-aniline and amino-phenol moieties at the end of the study. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC)

calculations) were carried out for the metabolites MHPC and 3-methylaniline (*m*-toluidine) using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For the active substance phenmedipham and 3-methylaniline (*m*-toluidine) also step 3 (FOCUS, 2001), $PEC_{SW/sed}$ calculations were available. FOCUS Step 4 calculations considering different buffer zones in combination with mitigation by drift reducing nozzles were conducted based on the Step 3 results for phenmedipham and 3-methylaniline. The Step 4 calculations following the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones being together with drift reduction nozzles were implemented in the values used for the risk assessment (only values leading to a realistic spray drift mitigation up to 95% are reported in Appendix A). The SWAN tool (version 1.1.4) was used to implement these mitigation measures in the simulations.

The groundwater exposure assessments were carried out using FOCUS (FOCUS, 2009) scenarios and the models PEARL v.4.4.4, PELMO v.5.5.3 and MACRO v.5.5.4 (Châteadun) for the active substance phenmedipham and metabolite MHPC. The potential for groundwater exposure from the representative uses by phenmedipham and MHPC 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 and groundwater, when surface water or groundwater 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).

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[5], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to European Commission (2002a), the risk to adult honeybees from chronic toxicity and the risk to bee brood could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Phenmedipham was discussed at the Pesticides Peer Review Experts' Meeting 169 (October 2017).

It is considered that insufficient information was provided to demonstrate the compliance of the batches used in the (eco)toxicity studies compared to the technical specification, and therefore, this issue was identified as critical area of concern.

The first tier risk assessment to **birds and mammals** indicated a low acute risk from dietary exposure for all representative uses. The long-term risk to birds was concluded low for representative use in sugar beet/fodder beet with the worst-case use pattern of three applications at 320 g a.s./ha; therefore, it could be considered low for all representative uses.

The experts at the Pesticides Peer Review Meeting 169 (ecotoxicology) concluded that it was not possible to define an endpoint for long-term risk to mammals considering the read-across with desmedipham and without having information on reproduction parameters (data gap). Therefore, the long-term risk assessment to mammals could not be performed for all the representative uses in sugar beet/fodder beet (data gap and assessment not finalised).

The risk from secondary poisoning was not triggered (log $P_{ow} < 3$) and the risk to birds via consumption of contaminated water was assessed as low.

For **aquatic organisms**, toxicity data with the active substance were available on fish, aquatic invertebrates including sediment-dwelling organisms and aquatic macrophytes. Ecotoxicity data on algae are missing for the active substance (data gap). Being algae the most likely risk assessment driver in the aquatic system due to the herbicidal activity of phenmedipham, the risk assessment cannot be finalised.

[5] 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.

With regard to the pertinent aquatic metabolites in the surface water and sediment compartment, several ecotoxicity data with MHPC and 3-methylaniline (*m*-toluidine) were available on aquatic organisms.

The acute risk assessment for fish, aquatic invertebrates, sediment-dwelling organisms and aquatic macrophytes is low for all representative uses for phenmedipham.

The chronic risk assessment for the worst-case representative use in sugar beet (3 × 320 g/ha) indicated that phenmedipham is of high risk for aquatic invertebrates in two of four FOCUS Step 4 exposure scenarios even considering mitigation options (no-spray buffer zones and vegetated buffer strips up to 20 m) and also in one of four FOCUS Step 4 scenarios considering mitigation options (no-spray buffer zones and vegetated buffer strips up to 20 m) for the use pattern that includes two applications at 320 g/ha (data gap). No chronic risk has been identified for invertebrates following the use pattern of one application at 320 g/ha when using mitigation measures up to 20 m. To add-on, the chronic risk to fish is low if mitigation measures are considered (no-spray buffer zones and vegetated buffer strips up to 20 m) for the worst-case use in sugar beet.

The risk assessment indicated that MHPC is of low risk to aquatic organisms except to aquatic invertebrates (chronic), where, for the worst-case, representative use in sugar beet followed by three applications at an application rate of 320 g a.s./ha, the risk assessment indicated high risk in a screening step. No risk assessment was performed for the use patterns that include one and two applications (data gap).

For the worst-case representative use, the risk assessment from 3-methylaniline (*m*-toluidine) fails to aquatic invertebrates in two of 4 FOCUS Step 3 scenarios (acute and chronic). Low risk to aquatic invertebrates is confirmed by using mitigation option measures as follows: no-spray buffer zones and vegetated buffer strips up to 20 m.

Acute contact and oral toxicity studies on **honeybees** were performed with the active substance and the formulated product. Furthermore, a 10-day chronic laboratory study with a phenmedipham-based formulated product was available. The available ecotoxicity study with bumblebees showed that the active substance is equally toxic for bumblebees as for honeybees in a contact acute scenario; however, oral toxicity data to bumblebees is not available. According to EFSA (2013), low risk has been identified to honeybees from contact exposure for all representative uses. High risk has been identified in the oral chronic scenario due to weeds and in the treated crop. However, since the use patterns are applicable at early growth stage of the crop, the chronic risk to bees in the treated crop can be considered low unless Member States granted authorisations for seed production; in that case, this risk should be further considered. Likewise, since phenmedipham is particularly used for the control of a wide range of broad-leaved weeds, the exposure via contaminated weeds could be considered of low relevance for the uses according to the GAPs reported.

The acute and chronic risk through exposure via residues in guttation fluid and via surface water was assessed as low in pertinent lower tier risk assessments according to EFSA (2013). However, the risk to bees should be evaluated for the puddle scenario (data gap). For honeybee larvae, a tier 1, risk assessment was not available due to the lack of a suitable endpoint according to the EFSA, 2013. An Oomen et al. (1992) feeding test was available and no effects were observed; however, these kinds of studies are considered not suitable for risk assessment according to the EFSA, 2013 (data gap). Insufficient information was available to perform a risk assessment for sublethal effects (i.e. hypopharyngeal glands (HPG), data gap) and accumulative effects. The risk from exposure to metabolites occurring in pollen and nectar from the representative uses in sugar beet is considered low provided that the use is at early stage of the sugar beet and assuming no seed production. Data to perform a risk assessment for solitary bees were not available, and for bumble bees only, the acute contact exposure scenario has been confirmed to be of low risk.

As regards to **other non-target arthropods**, laboratory studies were available with the standard indicator species and the formulated product. No additional test species were tested at tier 1 but at higher tiers. On the basis of a risk assessment with the standard tier 1 indicator species, a high in-field risk to non-target arthropods was indicated for the representative worst case use of three applications on sugar beet/fodder beet. No off-field risk from phenmedipham uses has been identified. A number of higher tier studies (extended laboratory and aged residue studies) with different arthropod species were available. These studies confirmed that a high initial in-field risk can be refined; therefore, low risk to non-target arthropods was concluded according to the representative worst case use.

Effects on non-target **soil meso- and macrofauna** (i.e. earthworms, collembolan and soil predatory mites) have been tested with the active substance, the formulated product, the metabolite MHPC and as additional information, the metabolite 3-methylaniline (*m*-toluidine) was tested (only one

earthworms' test study). In the first tier, low risk has been identified for all in-soil communities including **soil microorganisms** based on the representative worst-case use of three applications at an application rate of 320 g a.s./ha.

Low risk was identified on **non-target terrestrial plants** and for organisms involved in **biological methods for sewage treatment**.

Regarding the **potential for endocrine disruption** of phenmedipham, all the available information was discussed by the experts at the Pesticides Peer Review Experts' Meeting 169 (ecotoxicology) and at the Pesticides Peer Review Experts' Meeting 168 (mammalian toxicology). For the ecotoxicological assessments, no other studies were available to address the potential endocrine activity of phenmedipham. 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 phenmedipham on terrestrial and aquatic vertebrates.

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
Phenmedipham	Low to high (DT_{50} = 4.2–139.5 days)	Low risk to in-soil communities
MHPC	Low to moderate (DT_{50} = 8.0–22.2 days)	Low risk to in-soil communities

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
Phenmedipham	Low (K_{Foc} = 918–1618 mL/g)	FOCUS GW: No	Yes	Yes
MHPC	High to very high (K_{Foc} = 31–73 mL/g)	FOCUS GW: No	Data not needed	Yes Based on the carcinogenic and developmental toxicity, classification proposed by the peer review (cat 2) and potential genotoxicity of the parent

(a)FOCUS scenarios or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Phenmedipham	High-chronic risk to aquatic invertebrates for the use pattern with two and three applications Low risk to aquatic organisms for the use pattern that includes one application Risk assessment cannot be finalised due to missing data on algae
MHPC	High-chronic risk to aquatic invertebrates other than sediment organisms
3-methylaniline (*m*-toluidine)	Low acute and chronic risk to aquatic organisms with mitigation measures

Table 4: Air

Compound (name and/or code)	Toxicology
Phenmedipham	> 7.0 mg/L air/4h (nose only) – no classification required

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 search of the scientific peer-reviewed open literature on the active substance and its metabolites relevant to consumer exposure, dealing with side effects on health and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011). Details on the search performed on the active substance also need to be included in the RAR (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown, see Section 2).
- Spectra for identification of the relevant impurities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Content of relevant impurities, before and after storage (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- A method for determination of the relevant impurities in the representative formulation (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Information on which analytical method has been used in each of the toxicological studies is missing (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Toxicological information to address the toxicological relevance of most impurities present in the technical specifications from both applicants (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Toxicokinetic data in rodents are needed to complete the toxicity profile of phenmedipham (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Skin sensitisation study performed with the active substance (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Data for the phototoxicity evaluation in the area of UVB wavelength (no validated method exists) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- *In vivo* follow-up to positive chromosome aberration tests observed *in vitro* with phenmedipham (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Reproductive toxicity has not been adequately addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Mechanistic data such as level 2 and 3 of the OECD conceptual framework and analysed according to the EFSA Scientific Opinion on the hazard assessment of endocrine disruptors related to the observed pituitary, uterus, prostate, testis and adrenals effects in order to address a potential endocrine disruptive-mediated MoA (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Acute toxicity studies on the representative plant protection product or equivalent formulation have not been provided (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Genotoxicity data on plant/livestock metabolites 3-aminophenol, 3-acetamidophenol, 4-acetamido-*o*-cresol, 4-aminocresol, acetamido-benzoic acid, aminobenzoic acid and *m*-acetotoluidine and, pending on further assessment in the residue section, repeated-dose toxicity data relevant to consumer exposure may be needed. In addition, genotoxicity and repeated-dose toxicity data relevant to consumer exposure are needed for 3-methylaniline (*m*-toluidine) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Data to exclude the possible formation of MHPC and 3-methylaniline (*m*-toluidine) in sugar and sugar beets by-products, used as feed item for animal, has to be also investigated (relevant for the uses on sugar beet; submission date proposed by the applicant: unknown; see Section 3).

- Sufficient number of residue trials (four NEU and eight SEU) compliant with the representative GAPs and analysed according to the proposed residue definition for risk assessment have to be provided (relevant for all representative uses submission date proposed by the applicant: unknown; see Section 3).
- Animal feeding studies covered by valid storage stability data and analysed according to the residue definition for risk assessment for animal commodities, except poultry, (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 3).
- Information on the substances resulting from water treatment processes on the residues of phenmedipham (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to define the ecotoxicological relevant endpoint to mammals is needed (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to perform the long-term risk to mammals from phenmedipham (relevant for all the representative uses in sugar beet/fodder beet; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the chronic risk to aquatic invertebrates from phenmedipham (relevant for the representative uses in sugar beet that include 2 or 3 applications at 320 g/ha; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to the aquatic invertebrates from MHPC (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to the algae community from phenmedipham (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to bees from exposure via the puddle scenario (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to bee larvae (relevant for all the representative uses in sugar beet; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk from sublethal effects on bees (i.e. HPG) (relevant for all the representative uses in sugar beet; 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

- No-spray buffer zones and vegetated buffer strips up to 20 m are necessary to achieve low chronic risk to aquatic vertebrates (fish) in FOCUS Step 4 R3/stream scenario for phenmedipham.
- No-spray buffer zones up to 10 m are necessary to achieve low chronic risk to aquatic invertebrates in FOCUS Step 4 D3/ditch and D4/stream scenarios for phenmedipham.
- No-spray buffer zones and vegetated buffer strips up to 20 m are necessary to achieve low chronic risk to aquatic invertebrates in FOCUS Step 4 R1/stream for the use pattern of phenmedipham including two applications.
- No-spray buffer zones and vegetated buffer strips up to 20 m are necessary to achieve low chronic risk to aquatic invertebrates in FOCUS Step 4 R/stream for the use pattern of phenmedipham including 1 application.
- No-spray buffer zones and vegetated buffer strips up to 20 m are necessary to achieve a low acute risk to aquatic invertebrates in R1/stream and R3/stream scenarios for the metabolite 3-methylaniline (*m*-toluidine).
- No-spray buffer zones and vegetated buffer strips up to 20 m are necessary to achieve a low chronic risk to aquatic invertebrates in R1/stream and R3/stream scenarios for the metabolite 3-methylaniline (*m*-toluidine).

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[6] 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) Non-dietary exposure risk assessment cannot be conducted since reference values could not be established (see Section 2).
2) The consumer risk assessment cannot be finalised as, due to non-conclusion for genotoxicity, reference values could not be established (see Section 3).
3) The consumer risk assessment cannot be finalised with regard to processed commodities and pending upon the comprehensive livestock assessment (see Section 3).
4) Consumer risk assessment could not be finalised in relation to the substances resulting from water treatment processes on the residues of phenmedipham (see Section 4).
5) Long-term risk to mammals could not be finalised (see Section 5).
6) Aquatic risk assessment could not be finalised (algae) (see Section 5).

9.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of 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.

7) The technical specifications proposed by either of the applicants, including the original one from Bayer, are not covered by the batches used in the key toxicological studies (see Sections 2 and 5).
8) Due to the lack of adequate follow-up *in vivo* to the clastogenic effects observed *in vitro* with phenmedipham, toxicological reference values cannot be established; in addition, the reproductive toxicity potential of the active substance could not be characterised (see Section 2).
9) Phenmedipham is listed in Annex VI of Regulation (EC) 1272/2008 and no classification for human health is included. The developmental toxicity studies were available in the original dossier, but EFSA does not have information regarding the assessment of carcinogenicity and developmental toxicity by the ECB regarding the consideration of the substance under the previous regulatory frame for classification and labelling. Following the present re-evaluation, the peer review proposed a classification as carcinogen Category 2 (a new related study was submitted), and as developmental toxicity Category 2 (for developmental

[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.

effects observed in previously evaluated studies). Based on this proposal, 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 ED properties are met. In addition, an ED-mediated mode of action for the effects observed in the pituitary, uterus, prostate, testis and adrenals, supported by ToxCast data could not be ruled out (see Section 2).

9.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

In addition to the issues identified in Sections 9.1 and 9.2, all columns are grey, as the technical material specification proposed was not comparable to the material used in the testing that would be used to derive the toxicological reference values.

Table 5: Overview of concerns

Representative use		Sugar beet/fodder beet, max 320 g a.s./ha	Sugar beet/fodder beet, max 2 × 320 g a.s./ha	Sugar beet/fodder beet, max. 3 × 320 g a.s./ha
Operator risk	Risk identified			
	Assessment not finalised	X[1]	X[1]	X[1]
Worker risk	Risk identified			
	Assessment not finalised	X[1]	X[1]	X[1]
Resident/ bystander risk	Risk identified			
	Assessment not finalised	X[1]	X[1]	X[1]
Consumer risk	Risk identified			
	Assessment not finalised	X[2,3,4]	X[2,3,4]	X[2,3,4]
Risk to wild non-target terrestrial vertebrates	Risk identified			
	Assessment not finalised	X[5]	X[5]	X[5]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified			
	Assessment not finalised			
Risk to aquatic organisms	Risk identified		1/4 FOCUS scenarios	2/4 FOCUS scenarios
	Assessment not finalised	X[6]	X[6]	X[6]
Groundwater exposure to active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure to metabolites	Legal parametric value breached[(a)]			
	Parametric value of 10 µg/L[(b)] breached			
	Assessment not finalised			

Columns are grey if no safe use can be identified. The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.

(a): 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

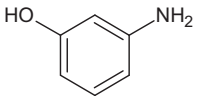
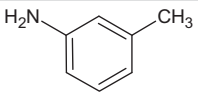
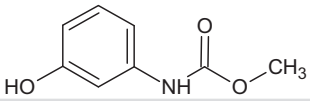
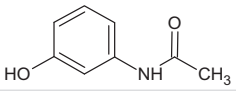
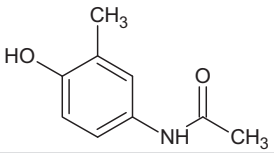
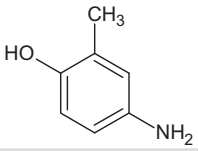
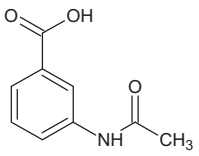
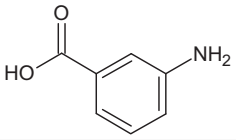
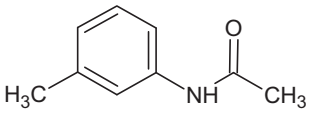
a.s.	active substance
ADI	acceptable daily intake
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CA	chromosomal aberration
CHO	Chinese hamster ovary
CF	Conversion factor
CLP	classification, labelling and packaging
co-RMS	co-rapporteur Member State
DFG	Deutsche Forschungsgemeinschaft method
ED	endocrine disrupting
DT_{50}	period required for 50% dissipation (define method of estimation)
(ECB)	European Chemicals Bureau
ECHA	European Chemicals Agency
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HPG	hypopharygeal glands
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LLNA	local lymph node assay
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MN	micronucleus
MoA	mode of action
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PBIs	plant back intervals
PEC	predicted environmental concentration
PEC_{sed}	predicted environmental concentration in sediment

PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
P_{ow}	partition coefficient between *n*-octanol and water
ppm	parts per million (10^{-6})
PPP	plant protection product
PT	proportion of diet obtained in the treated area
QC	quality control
QuEChERS	Quick Easy Cheap Effective Rugged Safe
RAR	Renewal Assessment Report
RMS	rapporteur Member State
RP/HPLC-UV	reversed phase high performance liquid chromatography with UV detector
SE	suspo-emulsion
SMILES	simplified molecular-input line-entry system
TRR	total radioactive residue
UF	uncertainty factor
UVB	ultraviolet B

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5151

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation	Structural formula
3-aminophenol	3-aminophenol OC1=CC=CC(N)=C1	
3-methylaniline (*m*-toluidine)	3-methylaniline CC1=CC=CC(N)=C1	
MHPC	methyl (3-hydroxyphenyl)carbamate Oc1cccc(NC(=O)OC)c1	
3-acetamidophenol	*N*-(3-hydroxyphenyl)acetamide Oc1cccc(NC(C)=O)c1	
4-acetamido-*o*-cresol	*N*-(4-hydroxy-3-methylphenyl)acetamide Cc1cc(NC(C)=O)ccc1O	
4-aminocresol	4-amino-2-methylphenol Nc1ccc(O)c(C)c1	
acetamido-benzoic acid	3-acetamidobenzoic acid O=C(C)Nc1cc(ccc1)C(=O)O	
aminobenzoic acid	3-aminobenzoic acid OC(=O)c1cc(N)ccc1	
***m*-acetotoluidine**	*N*-(3-methylphenyl)acetamide O=C(C)Nc1cc(C)ccc1	

SMILES: simplified molecular-input line-entry system.
(a): The compound name in bold is the name used in the conclusion.