CONCLUSION ON PESTICIDES PEER REVIEW

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

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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 desmedipham 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 desmedipham 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: desmedipham, 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. Desmedipham 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 Desmedipham, comprising of UPL Europe Ltd and Bayer CropScience AG, for the renewal of approval of the active substance desmedipham. 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 desmedipham 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 Desmedipham, 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 desmedipham 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 desmedipham 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 desmedipham 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 relevant metabolites in the mammalian toxicology, environmental fate and behaviour and ecotoxicology areas.

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, for a method for determination of the relevant impurities in the representative formulation, for either demonstration of the validity of the existing methods for monitoring of the conjugated desmedipham in food and feed of plant origin or for a new monitoring method for all components of residue definition in plant commodities and for additional validation data to demonstrate the validity of the existing method for monitoring of the sulfate conjugate of EHPC or a new monitoring method for all components of the residue definition in body fluids.

In the mammalian toxicology area, data gaps were identified in relation to skin sensitisation, possible phototoxicity within ultraviolet B (UVB) wavelength, the need for genotoxicity and repeated dose toxicity data relevant to consumer exposure for the metabolites 3-aminophenol, 3-acetamidophenol and 4-acetamidophenol, and data to address the toxicological relevance of most impurities present in the technical specifications from both sources. The plant metabolites 4-aminophenol and aniline are classified according to Reg. 1272/2008 (harmonised classification) as category 2 mutagens and category 2 carcinogen for aniline; they are therefore of toxicological concern. A critical area of concern has been identified as the conditions of the interim provisions of Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are met for desmedipham according to the its proposed classification regarding carcinogenicity and reproductive toxicity category 2 (for both reproduction and developmental toxicity) by the peer review (but not according to the harmonised classification); in addition, adverse effects observed on the thyroid in the 2-year study in rats indicate that a potential for endocrine disruption of desmedipham cannot be ruled out, and further clarification is needed using mechanistic data.

In the area of residues, several data gaps were identified leading to the situation that the residue definitions in plant and livestock commodities could not be finalised. Residue trial data were insufficient to address the residue levels in commodities for human and animal consumption according to the residue definition for risk assessment and monitoring. Therefore, maximum residue levels (MRLs) could not be derived and a preliminary consumer risk assessment could not be conducted. Moreover, based on the currently available data and information, dietary exposure of consumers and/or livestock to residues containing aniline (free or conjugated) and consumer exposure to 4-aminophenol via animal commodities cannot be excluded which has to be considered a concern in the absence of data that may permit higher tier risk assessments to be conducted.

With respect to fate and behaviour in the environment, the data needed to perform the exposure assessment were available except for reliable batch adsorption studies with metabolite EHPC. Therefore, a data gap has been identified during the peer review for reliable soil adsorption data for EHPC, leading to the groundwater exposure assessment for this metabolite not finalised. 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 long-term risk to birds and mammals, the risk to algae, the risk to bees and the possible endocrine disrupting properties of desmedipham. The long-term risk to mammals was indicated as a critical area of concern since it was related to all representative uses.

Table of contents

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 Desmedipham, comprising of UPL Europe Ltd and Bayer CropScience AG, for the renewal of approval of the active substance desmedipham. 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 desmedipham 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 Desmedipham, 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 desmedipham as a post-emergence herbicide on sugar beet/fodder beet, as proposed by the applicants. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

[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 (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

Desmedipham is the ISO common name for ethyl 3-phenylcarbamoyloxycarbanilate (IUPAC).

The representative formulated product for the evaluation was 'Desmedipham 160 + Phenmedipham 160', an emulsifiable concentrate (EC) containing 160 g/L desmedipham and 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. 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 desmedipham 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 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). In particular, a detailed assessment of all studies found relevant or of unclear relevance in the mammalian toxicology, and fate and behaviour section needs to be provided. Detailed summary and assessment of relevance/reliability need to be added to the summary dossier and evaluated by the RMS in the RAR. Detailed information such as exclusion criteria should be presented, studies needing an assessment based on full text documents should be provided and their assessment summarised in the RAR. For ecotoxicology, details on whether the search was performed to cover all the data requirement points and in particular to capture data on effects on amphibians and reptiles should also be included (see Section 7).

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 980 g/kg (Bayer) and 970 g/kg (UPL). Toluene (Bayer only), 3-aminophenol and aniline are considered relevant impurities with a maximum content of 2 g/kg, 1 g/kg and 0.5 g/kg, respectively. It should be noted that the relevance of other impurities is not concluded (see Section 2). There is no FAO specification available for desmedipham.

The batches used in the (eco) toxicological assessment support the new reference specification but not the original one (See Sections 2 and 5); as a consequence, it is proposed to update the reference specification.

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 desmedipham or the representative formulation; however, data gaps were identified for spectra for the relevant impurities and for the content of the relevant impurities before and after storage. The main data regarding the identity of desmedipham 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 analytical method for determination of the relevant impurities in the plant protection product.

Desmedipham (free) can be monitored in food and feed of plant origin by the multiresidue method DFG S19 (extended revision) using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with a limit of quantification (LOQ) of 0.01 mg/kg in each commodity group. In addition, there is QuEChERS method using gas chromatography with mass spectrometry (GC-MS) and/or liquid chromatography with tandem mass spectrometry (LC-MS/MS) for all plant commodities with LOQs in the range 0.01–0.02 mg/kg. However, the residue definition was concluded as desmedipham free and conjugated (see Section 3). As a consequence, a data gap was identified for either demonstration of the validity of the existing methods for monitoring of the conjugated desmedipham or for a new monitoring method for all components of the residue definition in plant commodities. It should be noted that a residue definition for monitoring in plant processed commodities is proposed (see Section 3). 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. A validated QuEChERS method using HPLC–MS/MS with a LOQ of 0.01 mg/kg exists for monitoring of desmedipham residues (desmedipham and EHPC) in food of animal origin. However, it should be mentioned that the residue definition for animal products is not concluded and new monitoring methods might be required (see Section 3).

Desmedipham residues (desmedipham and EHPC) in soil can be monitored by DFG method S 19 (extended revision) with HPLC-MS/MS with a LOQ 0.01 mg/kg.

Appropriate HPLC-MS/MS method exists for monitoring of desmedipham residues (desmedipham and EHPC) in water with a LOQ of 0.05 μg/L. Desmedipham residues in air can be monitored by Reversed phase high performance liquid chromatography with UV detector (RP/HPLC-UV) or LC-MS/MS with LOQs of 10 $\mu g/m^3$ and 0.5 $\mu g/m^3$, respectively.

LC–MS/MS method with a LOQ of 50 μg/L can be used for monitoring of desmedipham and EHPC in body fluids. However, the residue definition for monitoring in body fluids was concluded as desmedipham, EHPC and its sulfate conjugate, and as a consequence, a data gap for additional validation data to demonstrate validity of the existing method for monitoring of the sulfate conjugate of EHPC or a new monitoring method for all components of the residue definition in body fluids was identified. QuEChERS method with LC–MS/MS with a LOQ of 0.01 mg/kg is available for monitoring of desmedipham and EHPC in body tissues. However, it should be mentioned that the residue definition in body tissues is open and new monitoring methods might be requested.

2. Mammalian toxicity

The toxicological profile of the active substance desmedipham was discussed at the Pesticides Peer Review Experts' Meeting 168 (session 1, 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 CLP Criteria (ECHA, 2015).

The technical specification from UPL and the newly proposed technical specification from Bayer are supported by the (eco)toxicological assessment, but not the one previously set during the EU Annex I inclusion of 2005 since the levels of four impurities are too high including the relevant impurity, aniline. The toxicological relevance of most impurities present in the technical specifications has not been sufficiently addressed for both sources (data gap). Toluene is a relevant impurity (Bayer only), but its maximum level proposed for the technical specifications (2 g/kg) is not of toxicological concern. Aniline and 3-aminophenol are also relevant impurities due to their harmonised classification as genotoxic

carcinogen Cat. 2 and as harmful if swallowed and if inhaled, respectively, and their maximum levels in the technical specifications should not exceed 0.5 g/kg and 1 g/kg.

Desmedipham absorption is relatively fast and extensive (about 80% in 24 h). Desmedipham is widely distributed with higher amounts in blood, plasma, liver, lungs, kidneys, heart, spleen, ovaries, testes, thyroids and adrenals. In general, radioactivity levels in female tissues were higher than those observed in males. Around 90% of desmedipham is excreted within 24 h, mainly via urine. Desmedipham is rapidly metabolised in the rat via oxidative/hydrolytic cleavage of the parent molecule, hydroxylation of aromatic ring structures, acetylation of amine groups and conjugation. Unchanged parent is only observed in faeces after high-dose administration. In the comparative interspecies (rat and human) metabolism study *in vitro*, significant differences or human-specific metabolites were not observed. Since the metabolites EHPC and its sulfate conjugate have been identified as major metabolites in rats, they should be included in the residue definition for monitoring in body fluids (blood and urine) in humans together with the parent desmedipham.

Low acute toxicity was observed when desmedipham 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 desmedipham to cause skin sensitisation cannot be drawn due to severe limitations in the studies submitted (data gap). Desmedipham 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 desmedipham. However, no validated methods are available to address properly UVB absorbers (data gap).

In all short-term rodent's studies (rats and mice), the critical effects observed were related to haemolytic anaemia (increase of the methaemoglobin (MetHb) and other haematological parameters and increased haematopoiesis in spleen), leading to an overall short term no-observed adverse effect level (NOAEL) of 2.6 mg/kg body weight (bw) per day for rats and 22 mg/kg bw per day for mice. An acute NOAEL of 5.2 mg/kg bw per day has been identified from the 90-day rat study for the increase in MetHb. In one of the rat studies, follicular cell hypertrophy in thyroids was also observed at the lowest observed adverse effect level (LOAEL). In dogs, the critical effects were related to the thyroids and to haemolytic anaemia (changes in haematological parameters and increased haematopoiesis in the bone marrow). The overall NOAEL for dogs from the 90-day and 1-year studies was 9.7 mg/kg bw per day based on thyroid follicular epithelial hypertrophy in thyroids and increased thyroid weight. Desmedipham gave positive results *in vitro* for both gene mutation in mammalian cells and chromosomal aberrations; these results were not confirmed *in vivo* and desmedipham is therefore unlikely to be genotoxic *in vivo*. Investigation of photomutagenicity is not required as at wavelengths above 290 nm the molecular extension coefficient is below 1,000 L mol^{-1} cm^{-1}. The systemic NOAEL of the long-term carcinogenicity rat study (2 years) is 3.2 mg/kg bw per day based on increase in MetHb and effects in spleen, liver, kidney and thyroid. The RMS disagreed, considering this dose as rather being a LOAEL. The long-term systemic NOAEL for the 2-year mice study was at 22 mg/kg bw per day based on haematological effects and liver toxicity. Carcinogenicity was not observed in the long-term carcinogenicity studies in rats and a carcinogenicity NOAEL is set above 80 mg/kg bw per day. In the long-term carcinogenicity studies in mice, pulmonary and ovarian tubular adenomas were observed with a NOAEL for carcinogenicity below 5.8 mg/kg bw per day; on this basis, the experts considered that classification regarding carcinogenicity according to the criteria of Regulation (EC) 1272/2008[3] (Carc 2, H351) may be appropriate.[4] The mechanism of carcinogenicity has not been investigated.

Three multigenerational reproductive studies in rats were submitted for desmedipham. The parental NOAEL is 4 mg/kg bw per day based on reduced body weight and haemolytic anaemia (effects in spleen). The reproductive NOAEL is 4 mg/kg bw per day based on decreased total cauda sperm number and the NOAEL for offspring's toxicity is 4 mg/kg bw per day based on reduced litter size in F2a and F2b pups. Nine developmental studies (five oral in rat, three oral in rabbits and one dermal in rabbits) were provided. For rats, the overall maternal NOAEL is 7 mg/kg bw per day based on methaemoglobinaemia, while the developmental NOAEL is 10 mg/kg bw per day based on increased incidences of palatoschisis, micrognathia, agnathia and open eyes and occurrence of cleft palate and visceral effects. In rabbits, the maternal and developmental NOAEL is 30 mg/kg bw per day based on reduced maternal body weight

[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, 1-1355.

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

gain, increased incidences of early embryonic death and increase in slight caudal pelvic shift. Based on the effects observed on both the reproduction and the development in rats, the experts considered that classification regarding reproduction and development (Repro 2, H361fd) according to the criteria of Regulation (EC) 1272/2008 may be appropriate for desmedipham. The available data for desmedipham do not raise concern in relation to neurotoxicity and immunotoxicity.

Desmedipham is listed in Annex VI of Regulation (EC) 1272/2008 and no classification for human health is included. The carcinogenicity studies were available in the original dossier, but EFSA does not have information regarding the assessment of carcinogenicity, reproductive 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 carcinogenic Category 2 (no new studies submitted with regard to the previous evaluation) and as reproductive toxicity Category 2 (supported by new reproductive and developmental toxicity 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 potential on the basis of the thyroid effects observed could not be ruled out, and further clarification is needed using mechanistic data (data gap).

The acceptable daily intake (ADI) and acceptable operator exposure level (AOEL) are set at 0.016 mg/kg bw per day based on the NOAEL of 3.2 mg/kg bw per day of the 2-year rat study, and an uncertainty factor (UF) of 200 (an additional factor of two to allow for a sufficient margin of safety (MoS) to the observed adenomas with a LOAEL of 5.8 mg/kg bw per day). The use of an additional UF of 2 was proposed after the Pesticides Peer Review Experts' meeting by the RMS and EFSA considered the proposal appropriate. During a written procedure and the MSs consultation on the EFSA conclusion, no MS expressed disagreement with this approach. The acute reference dose (ARfD) and acute AOEL (AAOEL) are set at 0.05 mg/kg bw, based on the NOAEL of 5.2 mg/kg bw per day from the 90-day study on rats where adverse effects on methaemoglobin were observed after 4 weeks and applying an uncertainty factor of 100. The newly set reference values constitute a revision of those set during the first peer review (ADI = 0.03 mg/kg bw per day, ARfD = 0.1 mg/kg bw and AOEL = 0.04 mg/kg bw per day) (European Commission, 2004).

The non-dietary exposure (i.e. operator, worker, bystander and resident) to desmedipham formulation which contains also equal amount of phenmedipham was estimated. As the two active substances are structural analogues and exhibit in general the same critical effects, it is appropriate to consider both exposure to desmedipham alone and the cumulative exposure to both active substances. Since reference values could not be established for phenmedipham due to genotoxicity concerns, an exposure assessment for phenmedipham could not be performed. For the purpose of this calculation, the exposure for desmedipham was duplicated as a surrogate to roughly cover also phenmedipham. This approach however underestimates the risk due to (1) genotoxic potential of phenmedipham and (2) dermal absorption has not been determined for phenmedipham and default dermal absorption values would be appropriate for phenmedipham in this formulation. The dermal absorption values for desmedipham derived from an *in vitro* dermal absorption study on human skin for desmedipham were 1% for the concentrate, 2% for intermediate dose (2.4 g/L) and 8% for the low dose (0.5 g/L). The estimated operator exposure to desmedipham does not exceed the AOEL even when no personal protective equipment (PPE) is worn according to the German model; according to the EFSA calculator (EFSA, 2014a), operators should wear PPE (workwear, arms, body and legs covered, gloves during mixing and loading (M/L) and application) to avoid exceeding the AAOEL. PPE (working clothing) has also to be worn by workers to ensure that the AOEL is not exceeded according to the EFSA calculator, but according to the EUROPOEM II, the estimated worker exposure does not exceed the AOEL even when no PPE are worn. The estimated bystander and resident exposure remains below the AOEL/AAOEL irrespective of the model used. When considering the cumulative exposure of the two active substances present in the representative formulation, the estimated operator exposure remains below the AOEL according to the German model, even without wearing PPE, while PPE has to be worn according to the EFSA calculator to ensure that the AOEL/AAOEL are not exceeded. As concluded for the risk assessment performed on desmedipham alone, PPE has also to be worn by workers to ensure that the AOEL is not exceeded according to the EFSA calculator, but according to the EUROPOEM II, the estimated worker exposure does not exceed the AOEL even when no PPE is worn. The estimated exposure of bystander and residents (Martin et al., 2008) does not exceed the AOEL; this is the case also for the cumulative exposure assessment according to the EFSA calculator except from the resident children where the AOEL is exceeded (118.6% of the AOEL).

Toxicological studies have been submitted with the metabolite EHPC, which has been identified together with its sulfate conjugate as major rat metabolites detected in plants, livestock and soil. The reference values of desmedipham apply to these two metabolites. The metabolites 4-aminophenol and aniline are classified as mutagenic category 2 and aniline also carcinogenic category 2, and therefore, they are of toxicological concern to perform consumer exposure. Toxicological data relevant to consumer exposure (repeated-dose toxicity and genotoxicity) are needed on 3-aminophenol, 3-acetamidophenol and 4-acetamidophenol (data gap).

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

Primary crop metabolism of desmedipham was investigated following foliar application in sugar beet. Desmedipham was cleaved under formation of significant proportions of a metabolite bearing the ethylcarbamate moiety (EHPC, free and conjugated) while the counter-moiety resulting from the cleavage would be aniline and/or its derivatives. Aniline was identified in one metabolism study in immature roots and leaves. In a second study, upon mild hydrolysis, formation of components that may correspond to aniline/3-aminophenol was observed. The presence of anilines could neither be confirmed nor excluded in the other metabolism studies since it is unknown whether anilines remained adequately determinable until sample analysis in view of the prolonged sample storage in these studies (data gap). According to public literature, the interactions of anilines with natural products and biopolymers are complex. It is generally known that anilines show low recoveries during storage stability experiments after a very short period of time. Based on the available metabolism studies, the presence of anilines in primary root crops cannot be excluded which is considered a concern (see Section 2 for hazardous properties).

Rotational crop metabolism studies were conducted in wheat, radish, turnip, lettuce and Swiss chard. Aniline is assumed to be constantly formed during degradation of desmedipham in soil but was not recovered as a major soil metabolite and features a very short half-life in aerobic conditions. Hence, the potential uptake in crops grown after sugar beet might be limited. However, based on the available rotational crop data, the potential presence of aniline and the identity of conjugates present in rotational crops could not be assessed (data gap).

On the basis of the primary crop metabolism data in root crops upon foliar application, the residue definition for monitoring is proposed as desmedipham (free and conjugated) and the residue definition for risk assessment is provisionally set as 1) sum of desmedipham and EHPC, and their conjugates, expressed as desmedipham and separately 2) aniline (free and conjugated). Studies in other primary crops are not available that could have been considered when deriving the residue definitions. The definitions might be provisionally applicable to rotational crops, pending confirmation following submission of information that allows further specification of the relevant residues in rotational crops.

The residue definitions differ from the residue definitions tentatively set in plant commodities during the review of the existing MRLs as desmedipham only since metabolism data were insufficient at that time (EFSA, 2014b).

From the studies investigating the nature of residues during processing, significant to complete degradation of desmedipham into aniline and EHPC was observed under the standard conditions simulating industrial and household processing and under specific conditions representative of sugar processing. Hence, the relevant residues that might be expected in processed commodities are already covered by the provisional residue definition for risk assessment for raw agricultural commodities. If processed commodities should be monitored, it is proposed to consider desmedipham and EHPC and their conjugates, expressed as desmedipham as the most suitable marker compounds for residues, depending on the processing conditions applied.

The available critical GAP (cGAP)-conform residue trials in sugar beet analysed for desmedipham and EHPC but did not determine conjugated residues of both compounds which are expected to form a significant fraction of the residues. The residue trials do therefore not comply with the residue definitions for risk assessment and for monitoring in root crops. Moreover, with regard to the residue trials, storage stability of EHPC could not be demonstrated in sugar beet leaves for the relevant period

of sample storage since significant degradation of EHPC was observed in storage stability tests within 1 month of freezer storage. The residue levels of metabolite EHPC (free) in sugar beet leaves obtained from the residue trials are therefore not reliable. Storage stability was sufficiently demonstrated for desmedipham and EHPC residues in sugar beet roots and only for desmedipham sugar beet leaves.

The magnitude of residues in rotational crops was not studied and whether such residue trials may be necessary has to be assessed once the residue definition for risk assessment in rotational crops has been finalised. Moreover, depending on the full investigation of residues in rotational crops, information to further address the data requirement for residue data in pollen and bee products for human consumption might still be necessary (data gap).

Two non-good laboratory practice (GLP) processing residue trials on sugar beet were conducted with desmedipham while the main degradation products (EHPC, aniline) were not determined. In view of the potential risk for consumers and livestock, processing residue trials analysing aniline in food and feed processed sugar beet commodities with immediate analysis after sampling are required (data gap).

As the representative uses on sugar and fodder beet are relevant to animal feeding, livestock metabolism studies were submitted in ruminants and poultry. Desmedipham was intensively metabolised in the animals into EHPC and 3- and 4-aminophenol (see Section 2 for hazardous properties) and 3- and 4-acetamidophenol with subsequent conjugation. As for identified shortcomings of the availably studies, data gaps were identified for further clarification, reassessment and investigation with regard to livestock metabolism data, such as the necessity to sufficiently address the fate of the phenoxy moiety in animals if metabolism data are triggered by dietary burden calculations. A data gap for metabolism data was also identified for fish based on the potential fat solubility of parent (log $P_{OW} > 3$). Residue definitions in animal commodities could not be derived on the basis of the available data and information. Currently, reliable calculations of the animal dietary burden including fish cannot be conducted in view of insufficient data describing adequately the residue levels in raw and processed animal feed items resulting from the representative uses in sugar beet and fodder beet (data gaps).

Residue trial data are also insufficient to address the residue levels in commodities for human consumption according to the provisional residue definition for risk assessment and the monitoring definition. Therefore, MRLs could not be derived for sugar beet. A preliminary consumer risk assessment with regard to residues of desmedipham and EHPC including their conjugates in sugar beet and potential residues in animal commodities due to transfer via feed items derived from sugar beet and fodder beet could not be conducted. Moreover, based on the currently available data and information, dietary exposure of consumers and/or livestock to residues containing aniline (in free and/or conjugated form) cannot be excluded as well as consumer exposure to 4-aminophenol residues via animal commodities. This has to be considered a concern as for the toxicological properties (mutagen) of aniline and 4-aminophenol and in the absence of data that may permit higher tier risk assessments to be conducted.

4. Environmental fate and behaviour

Desmedipham was discussed at the Pesticides Peer Review Experts' Teleconference 151 (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, desmedipham exhibited low to high persistence, forming the metabolite EHPC, which exhibited very low to low persistence. Mineralisation of the ^{14}C aniline ring radiolabelled desmedipham to carbon dioxide accounted for a maximum of 46.4% applied radioactivity (AR) and the ^{14}C-phenoxy labelled for a maximum of 25.9% AR after 112 days. The formation of unextractable residues for the ^{14}C-aniline ring and the ^{14}C-phenoxy ring radiolabel accounted for maxima of 42.2% AR and 58% AR after 112 days, respectively. In anaerobic soil incubations, desmedipham exhibited very low to low persistence and produced the metabolites EHPC and aniline. Anaerobic conditions are not expected to prevail for the representative uses in sugar beet. Photolysis is not expected to contribute to the degradation of desmedipham in soil according to the available studies.

Field dissipation studies with desmedipham were available in Germany and USA (California and North Dakota) in the first authorisation dossier. These studies have been considered not reliable during the re-evaluation.

Desmedipham was immobile or exhibited slight to low mobility in soil. Stability of EHPC was not demonstrated in the batch adsorption studies performed with EHPC. Therefore, no reliable adsorption parameters are available for this metabolite and a data gap has been identified during the peer review.

In the available lysimeter studies of 3-year duration (application first 2 years) desmedipham and EHPC were not found in the leachates (LOQ = 0.05 μg/L). Total radioactivity in the leachate amounted up to 0.39 μg/L as yearly mean annual concentration (after 3 years with application the first 2 years). However, the concentration of the two unidentified discrete unknown radioactive components detected was < 0.02 μg/L.

At environmental relevant temperature and pHs ranges, desmedipham undergoes rapid aqueous hydrolysis under alkaline conditions but can be considered to be stable at acidic conditions. Photolysis in water is not expected to contribute to the degradation of desmedipham in aquatic environment. In laboratory incubations in dark aerobic natural sediment water systems (pH 6.2–9.05), desmedipham exhibited very low to low persistence, forming the major metabolites EHPC (max. ca. 100% AR in whole system at day 0, exhibiting low to medium persistence), phenol (max 14.8% in water, very low persistent, no kinetics calculated) and aniline (max. ca. 71.9% in whole system at day 0, exhibiting very low to moderate persistence). The unextractable sediment fraction was the major sink for the aniline and phenoxy rings ^{14}C radiolabel moieties, accounting for up to maxima 45.8% AR and 70.8% AR, respectively, at the end of the study. Mineralisation accounted for 66.4% AR and 36.2% AR for the aniline and phenoxy 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 EHPC, aniline and diphenyl urea 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 desmedipham and metabolite aniline, up to Step 3 (FOCUS, 2001), PEC in surface water/sediment ($PEC_{SW/sed}$) calculations were available.

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 desmedipham. The potential for groundwater exposure from the representative uses by desmedipham 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. For the metabolite EHPC, the data gap identified for reliable adsorption data in soil prevents the calculation of reliable PEC in ground water (PEC_{gw}) at the current stage, leading to a data gap to address the groundwater leaching potential of EHPC. Therefore, the groundwater exposure assessment cannot be finalised before the adsorption behaviour of EHPC has been established (see Section 9). 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.

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

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 high for the representative use in sugar beet/fodder beet when the use pattern includes two applications at 240 g/ha

[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.

and three applications at 160 g/ha (data gap). The end point for long-term risk to mammals was discussed at the Pesticides Peer Review Meeting 168 (mammalian toxicology) and the NOAEL of 4 mg a.s./kg bw per day was agreed. The long-term risk to mammals was concluded high for all the representative uses in sugar beet/fodder beet except for insectivorous mammals when the use pattern includes only one application. Residue decline data have been submitted to refine the tier 1 risk assessment for plant materials and arthropods. However, the experts at the Pesticides Peer Review Meeting 169 considered those data insufficient (data gap). The risk from secondary poisoning and 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, algae and aquatic macrophytes. Ecotoxicity studies were discussed in the Pesticides Peer Review Experts' Meeting 169. Several studies were disregarded due to the instability of desmedipham in the test system. Furthermore, due to the herbicidal activity of desmedipham, an additional algae test should be provided (data gap). Some ecotoxicity data were available for the pertinent surface water metabolites; where no ecotoxicity end points were available, the metabolites were assumed to be 10 times more toxic than the parent in a screening assessment. For diphenyl urea, the available data demonstrated that the toxophore of desmedipham is lost in diphenyl urea; therefore, for those taxa where no specific data were available, dyphenyl urea was considered equally toxic as the parent. The risk assessment indicated that desmedipham is of low risk for fish (acute and chronic), aquatic invertebrates including sediment-dwelling organisms, algae and aquatic macrophytes following FOCUS Step 3 scenarios for all the uses. However, being algae the risk assessment driver in the aquatic system, the risk assessment might need to be reconsidered once data on the additional algae species become available. A low risk for the metabolites was indicated for all the uses, except for diphenyl urea where high risk to aquatic invertebrates (chronic) and aquatic plants have been identified following a screening step (data gap).

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 desmedipham-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 are 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. Furthermore, since desmedipham is particularly used for the control of a wide range of broad-leaved weeds, the exposure to bees from contaminated weeds could be considered to be of low relevance for the uses according to the GAP reported.

The acute and chronic risk from 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 end point 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 crop 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 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 uses. No off-field risk from desmedipham use has been identified. A number of higher tier studies (extended laboratory and aged residue studies) with the two standard species and one additional test species were available. Based on these studies, a low risk to non-target arthropods can be confirmed for the representative uses.

Effects on **non-target soil meso- and macrofauna** (i.e. earthworms, collembolan and soil predatory mites) were investigated with the active substance, the formulated product and the metabolite EHPC. In the first tier, low risk has been identified for in-soil communities except for one

collembolan. A collembolan field study was available, and its results were discussed in the Pesticides Peer Review Meeting 169. A no observed effect concentration (NOEC) of 480 g/ha based on *Parisotoma notabilis* allowed to refine the risk assessment, resulting in a low risk. For earthworms, higher tier studies were considered unnecessary for all representative uses, however, were submitted. The available earthworms' field study has been discussed in the experts' meeting 169 and considered inadequate to be used in the risk assessment due to its low statistical power.

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

Regarding the potential for endocrine disruption of desmedipham, 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). The experts agreed that considering the data gap identified in Section 2 to further clarify the endocrine disrupting potential through the thyroid modality, additional information is needed to confirm that the current aquatic risk assessment covers amphibians (data gap).

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
Desmedipham	Low to high (DT_{50} = 9.4–216.2 days)	Low risk to in-soil organisms
EHPC	Very low to low (DT_{50} = 0.29–8.7 days)	Low risk to in-soil macro-organisms
Aniline (anaerobic conditions)	Low (anaerobic: DT_{50} = 2.2 days)	No data required since anaerobic conditions are not deemed relevant for the representative uses

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
Desmedipham	Low to immobile (K_{Foc} = 1909–5236 mL/g)	FOCUS GW: no	Yes	Yes
EHPC	Data gap	Data gap	Open	Yes It is assumed to share the carcinogenic, reproductive and developmental toxicity properties of the parent as it was found to be a major rat metabolite (proposed classification by the peer review as Carc 2 and Repro 2)

(a): FOCUS scenarios or relevant lysimeter

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Desmedipham	Low risk to aquatic organisms. Data gap on additional algae species.
EHPC	Low risk to aquatic organisms
Aniline	Low risk to aquatic organisms
Diphenyl urea	High risk to aquatic organisms

Table 4: Air

Compound (name and/or code)	Toxicology
Desmedipham	> 7.4 mg/L air/4 h (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 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) is required. In particular, a detailed assessment of all studies found relevant or of unclear relevance in the mammalian toxicology and fate and behaviour section needs to be provided. Detailed summary and assessment of relevance/reliability need to be added to the summary dossier and evaluated by the RMS in the RAR. Detailed information such as exclusion criteria should be presented, studies needing an assessment based on full text documents should be provided and their assessment summarised in the RAR. For ecotoxicology, details on whether the search was performed to cover all the data requirement points and in particular to capture data on effects on amphibians and reptiles should also be included (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2, 4 and 5).
- 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).
- Either demonstration of the validity of the existing methods for monitoring of the conjugated desmedipham in food and feed of plant origin or a new monitoring method for all components of the residue definition in plant commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Additional validation data to demonstrate validity of the existing method for monitoring of the sulfate conjugate of EHPC or a new monitoring method for all components of the residue definition in body fluids (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Toxicological information to address the toxicological relevance of most impurities present in the technical specifications from both sources (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 (however, no validated method is currently available) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Mechanistic data related to the observed thyroid effects in order to address possible endocrine disrupting potential of desmedipham (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Toxicological data are needed to address the genotoxicity and repeated-dose toxicity (relevant to consumer exposure) of the plant metabolites 3-aminophenol, 3-acetamidophenol and 4-acetamidophenol (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Clarification of the storage conditions of sugar beet samples from currently available residue trials (as whole crop or chopped/macerated/homogenised) along the entire process from harvest to final analysis and if applicable, appropriate data addressing the storage stability under the conditions the samples were kept (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Residue trials in sugar beet leaves and roots determining residues of desmedipham, EHPC and their conjugates, and supported by validated analytical methods should be provided. Time of analysis upon sampling should be adequate to ensure sufficient stability of the residues

(relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).

- Residue trials in sugar beet leaves and roots determining residues of aniline and its conjugates. Residue data should be supported by validated analytical methods and time of analysis upon sampling should be adequate to ensure sufficient stability of the residues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Storage stability of aniline and conjugated aniline in sugar beet commodities (RAC and processed) and in animal matrices, based on the outcome, reassessment of the reliability of the residue (metabolism) studies with regard to the determination of aniline/conjugatedaniline/ aniline derivatives as appropriate in plant and animal commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- A consolidated pathway for the metabolism in sugar beet including metabolites identified in all of the available studies (old and new metabolism studies) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Sufficiently robust conversion factors for sugar beet root and leaves to convert the residue definition from monitoring to risk assessment should be established. The factors should also be applicable to fodder beet (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Investigation regarding the potential presence of anilines and on the identity of conjugated residues in rotational crops (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Further evidence should be submitted to substantiate that formation and coextraction of aniline are not expected when sugar beets are processed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Sufficient processing residue trials analysing for all compounds included in the residue definition for risk assessment in food and feed processed commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- A livestock dietary burden calculation upon availability of sufficient data addressing residues in feed items relevant for the representative uses in accordance with the plant residue definition for risk assessment (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- If a ruminant metabolism study is triggered, a new study conducted with the phenoxy-labelled desmedipham in ruminant matrices is necessary to sufficiently address the fate and behaviour of EHPC and other phenoxy moiety metabolites (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- If a poultry metabolism study is triggered, a reassessment of the metabolism study conducted with aniline labelling should be done and a new metabolism study with phenoxy labelling is required (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Information on metabolism, distribution and expression of residues in fish or alternatively dietary exposure estimates for fish to demonstrate that such study is not triggered (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Depending on the full investigation of residues in rotational crops, information to further address the data requirement for residue data in pollen and in bee products for human consumption (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Applicant to provide information on the substances resulting from water treatment processes on the residues of desmedipham (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- A study following OECD 106 investigating adsorption/desorption of EHPC is needed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).

- New estimations of PEC_{gw} for soil metabolite EHPC will need to be presented once reliable adsorption end points for this metabolite become available (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- Further information to address the long-term risk to birds for desmedipham (relevant for the representative uses with two and three applications; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the long-term risk to mammals for desmedipham (relevant for all the representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to amphibians in current risk assessment scheme for aquatic organisms is necessary (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to aquatic organisms for diphenyl urea (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to algae (relevant for all 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 representative uses; 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 representative uses; 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

- According to the EFSA calculator, operators should wear PPE (workwear, arms, body and legs covered, gloves during M/L and application) to ensure that the AAOEL is not exceeded, even if the risk assessment is performed on desmedipham alone (see Section 2).
- According to the EFSA calculator, both desmedipham (alone) and cumulative assessment estimates indicate that working clothing has to be worn by workers re-entering treated fields to ensure that the AOEL is not exceeded (see Section 2).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[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) The residue definitions in plant and livestock commodities could not be finalised and residue data were insufficient to propose MRLs and to conduct preliminary dietary exposure estimates (see Section 3).
2) Consumer risk assessment could not be finalised in relation to the substances resulting from water treatment processes on the residues of desmedipham (see Section 4).
3) Potential groundwater contamination by soil metabolite EHPC could not be evaluated due to the lack of reliable soil adsorption end points for this metabolite (see Section 4).

[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.

9.2. 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.

4) The conditions of the interim provisions of Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are met for desmedipham according to its proposed classification regarding carcinogenicity and reproductive toxicity cat. 2 by the peer review (but not according to the harmonised classification); in addition, it is noted that, from a scientific point of view, an endocrine-mediated mode of action cannot be ruled out considering the adverse effects observed on the thyroid in the 2-year study in rats for which further clarifications are needed using mechanistic data (see Section 2).
5) A high long-term risk was identified to mammals (see Section 5).
6) Exposure of consumers and/or livestock to residues containing free and/or conjugated aniline (mutagen) and consumer exposure to 4-aminophenol residues (mutagen) via animal commodities cannot be excluded, and data that may permit conducting higher tier risk assessments are not available (see Section 3).

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

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

Table 5: Overview of concerns

Representative use		**Sugar beet/fodder beet, max. 240 g a.s./ha**	**Sugar beet/fodder beet, max. 2 x 240 g a.s./ha**	**Sugar beet/fodder beet, max. 3 x 160 g a.s./ha**
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	X[6]	X[6]	X[6]
	Assessment not finalised	X[1,2]	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[5]	X[5]	X[5]
	Assessment not finalised			

Representative use		Sugar beet/fodder beet, max. 240 g a.s./ha	Sugar beet/fodder beet, max. 2 x 240 g a.s./ha	Sugar beet/fodder beet, max. 3 x 160 g a.s./ha
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified			
	Assessment not finalised			
Risk to aquatic organisms	Risk identified			
	Assessment not finalised			
Groundwater exposure to active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure to metabolites	Legal parametric value breached[(a)]			
	Parametric value of 10 µg/L[(b)] breached			
	Assessment not finalised	X[3]	X[3]	X[3]

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

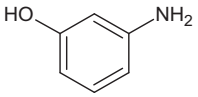
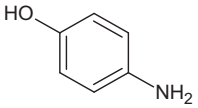
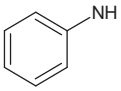
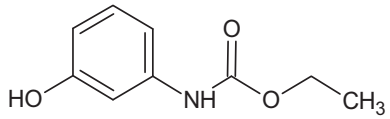
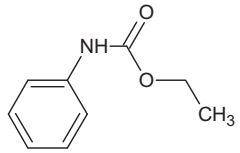
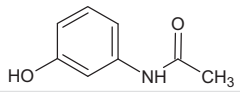
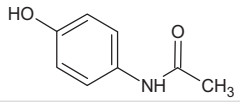
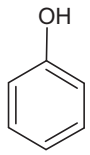
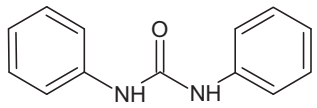
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
AR	applied radioactivity

ARfD	acute reference dose
bw	body weight
DFG	Deutsche Forschungsgemeinschaft method
DT_{50}	period required for 50% dissipation (define method of estimation)
GAP	Good Agricultural Practice
GC	gas chromatography
Hb	haemoglobin
HPLC-MS/MS	high-pressure liquid chromatography or high-performance liquid chromatography with tandem mass spectrometry
HPG	hypopharygeal glands
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
M/L	mixing and loading
mm	millimetre (also used for mean measured concentrations)
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PEC	predicted environmental concentration
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
PPE	personal protective equipment
PT	Phototoxicity or proportion of diet obtained in the treated area
QC	quality control
QuEChERS	Quick Easy Cheap Effective Rugged Safe
RAR	Renewal Assessment Report
RP/HPLC-UV	Reversed phase high performance liquid chromatography with UV detector
SE	suspo-emulsion
SMILES	simplified molecular-input line-entry system
UF	uncertainty factor
UV	Ultraviolet
UVB	Ultraviolet B
W/S	water/sediment
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2018.5150

Appendix B – Used compound codes

Code/trivial name[(a)]	Chemical name/SMILES notation	Structural formula
3-aminophenol	3-aminophenol OC1=CC=CC(N)=C1	
4-aminophenol	4-aminophenol Nc1ccc(O)cc1	
aniline (M15)	Aniline NC1=CC=CC=C1	
EHPC (M01)	ethyl (3-hydroxyphenyl)carbamate O=C(OCC)NC1=CC=CC(O)=C1	
phenyl urethane (M18)	ethyl phenylcarbamate O=C(OCC)Nc1ccccc1	
3-acetamidophenol	*N*-(3-hydroxyphenyl)acetamide Oc1cccc(NC(C)=O)c1	
4-acetamidophenol	*N*-(4-hydroxyphenyl)acetamide Oc1ccc(NC(C)=O)cc1	
phenol	phenol Oc1ccccc1	
diphenyl urea (M17)	*N*,*N*′-diphenylurea O=C(Nc1ccccc1)Nc2ccccc2	

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