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Updated peer review of the pesticide risk assessment of the active substance asulam (variant evaluated asulam-sodium)

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, the United Kingdom (France after Brexit), for the pesticide active substance asulam and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Regulation (EC) No 1107/2009 of the European Parliament and of the Council. The conclusions were reached on the basis of the evaluation of the representative use of asulam (variant evaluated asulam-sodium) as a herbicide on spinach and tulip, hyacinth and lily for bulb production. MRLs were assessed in spinach. The conclusions were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in February 2019. In addition, the peer review also provided considerations on whether exposure to humans and the environment from the representative uses of asulam-sodium can be considered negligible, taking into account the European Commission's draft guidance on this topic. The reliable endpoints, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified. An evaluation of data concerning the necessity of asulam-sodium as a herbicide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented.

Keywords: asulam, asulam-sodium, peer review, risk assessment, pesticide, herbicide, maximum residue level

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Summary

In accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council (hereinafter referred to as 'the Regulation'), the rapporteur Member State (RMS), the United Kingdom, received an application from UPL Europe Limited on 19 December 2013 for the approval of the active substance asulam-sodium. In accordance with Article 8(1)(g) of the Regulation, UPL Europe Limited submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 30 June 2014.

The RMS provided its initial evaluation of the dossier on asulam-sodium in the draft assessment report (DAR), which was received by the European Food Safety Authority (EFSA) on 21 April 2016. The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 6 July 2016 by dispatching the DAR for consultation to the Member States and the applicant, UPL Europe Limited.

Following consideration of the comments received on the DAR, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology. It became apparent during the peer review experts' meeting on residues that there is a need to obtain more information on several metabolites, which were identified in new metabolism studies, beyond what was available in the RMS's assessment report. The RMS was requested to provide a revised DAR for the sections on mammalian toxicology and residues. After the submission of the revised DAR in November 2017, EFSA organised a written commenting round with the Member States and following that an ad hoc expert consultation in the areas of mammalian toxicology and residues.

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

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of asulam (variant evaluated asulam-sodium) as a herbicide on spinach and tulip, hyacinth and lily for bulb production, as proposed by the applicant. MRLs were assessed in spinach. In addition, the conclusions from 2018 (EFSA Journal 2018;16(4):5251) were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in February 2019. Full details of the representative uses and the proposed MRLs can be found in Appendix B of this report.

Asulam-sodium has been concluded to meet the cut-off criteria for non-approval, Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 as amended by Commission Regulation (EU) No 2018/605 concerning endocrine-disrupting potential. The applicant provided further information to demonstrate that the exposure of humans to asulam-sodium was negligible under realistic conditions of use. Asulam-sodium is therefore being assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009 as amended by Commission Regulation (EU) No 2018/605. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of asulam-sodium to control a serious danger to plant health. The evaluation of the data concerned is presented in Appendices C and D of this conclusion.

Following completion of the peer review, the following conclusions are derived.

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

In the area of **identity, physical and chemical properties and analytical methods**, data gaps were identified for additional validation data for the residue monitoring method for plants, including its independent laboratory validation.

In the area of **mammalian toxicology and non-dietary exposure**, a critical area of concern was identified since asulam is considered to meet the criteria for endocrine disruption for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation 2018/605. Data gaps are identified concerning the available genotoxicity studies and dermal toxicity studies. As first tier for the negligible exposure assessment according to

the available draft Technical Guidance Document on assessment of negligible exposure, the operator exposure estimates are not exceeding 10% of the acceptable operator exposure level (AOEL). Worker exposure estimates exceed 10% of the AOEL for the use on flower bulbs, even with the use of gloves. Exposure estimates for residential children exceed 10% of the AOEL for both representative uses. As second tier, the margin of exposure for the critical effect is below 1,000 for workers for the use on flower bulbs; and for bystander and residential children for both uses.

In the area of **residues,** data gaps were identified for additional residue data in processed spinach commodities, information to validate the residue levels in the available processing trials regarding storage stability, and data on residues in rotational crops. These requirements are mostly affecting the finalisation of a robust consumer risk assessment for sulfanilamide and related compounds which are considered of higher potency than asulam.

Following the assessment if the provisions of negligible exposure according to Regulation (EC) 1107/2009 are met, it is concluded that uses on spinach for consumption, including pre and post emergence uses lead to residues above 0.01 mg/kg and above the limit of quantification (LOQ) of the analytical method and hence negligible dietary exposure cannot be assumed. In addition, the uses in spinach for seed cultivation and in tulip, hyacinth and lily for bulb production can involve rotation with edible crops, and consumer exposure to significant residues in rotational crops above 0.01 mg/kg and above the LOQ of the analytical method cannot be excluded based on the available information, while data to refine this assessment further are still pending.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the notable exception that information is missing regarding the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. Consequently, the consumer risk assessment from the consumption of drinking water could not be finalised. The potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L consequent to the uses assessed, was assessed as low for asulam and its salts and its soil metabolite sulfanilamide identified as triggering a groundwater exposure assessment, in geoclimatic situations represented by all seven pertinent FOCUS groundwater scenarios.

In the area of **ecotoxicology**, a data gap was identified to address the long-term risk to soil organisms from non-extractable soil residues (issue that could not be finalised). The long-term risk to birds and wild mammals was identified as a data gap and critical area of concern. In addition, due to high risk to aquatic organisms, a data gap was identified for the R4 FOCUS surface water scenario for the representative use for spinach.

Asulam-sodium is considered to meet the criteria for **endocrine disruption** for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605, leading to a critical area of concern. A conclusion on the endocrine-disrupting properties of asulam-sodium for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be made based on the information available.

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Background

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

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

The RMS, the United Kingdom (hereinafter referred to as the 'RMS'), in accordance with Article 7 of the Regulation, received an application from UPL Europe Limited on 19 December 2013 for a new approval of the active substance asulam-sodium. In accordance with Article 8(1)(g) of the Regulation, UPL Europe Limited submitted applications for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[2]. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 30 June 2014.

The RMS provided its initial evaluation of the dossier on asulam-sodium in the DAR, which was received by EFSA on 21 April 2016 (United Kingdom, 2016). The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 6 July 2016 by dispatching the DAR for consultation of the MSs and the applicant, UPL Europe Limited, for consultation and comments. EFSA also provided comments. In addition, EFSA conducted a public consultation on the DAR. The comments received were collated by EFSA and forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 12(3) of the Regulation were considered in a telephone conference between EFSA, the RMS, the European Commission and the European Chemicals Agency (ECHA) on 24 October 2016. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology.

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

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

It became apparent during the Peer Review experts' meeting on residues that there is a need to obtain more information on several metabolites, which were identified in new metabolism studies, beyond what was available in the RMS's assessment report. The RMS agreed to provide a revision of the DAR for the sections on mammalian toxicology and residues in order to address the outstanding issues and to provide a comprehensive assessment of the additional information submitted by the applicant following a request from EFSA in accordance with Art. 12(3) of the Regulation. The RMS submitted the revised DAR in November 2017. After the submission of the revised DAR EFSA organised

[1] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

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

a written commenting round with the MSs and following that an ad hoc expert consultation in the areas of mammalian toxicology and residues.

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

Commission Regulation (EU) 2018/605[3] introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the approval/renewal of active substances, including pending applications. The peer review on the active substance asulam-sodium was already completed at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the EFSA/ECHA (2018) guidance document[4] for this substance was not available.

Since on the basis of the EFSA Conclusion published on 20 April 2018, it was not possible for risk managers to conclude whether or not the active substance asulam-sodium is an endocrine disruptor, in February 2019 the European Commission requested EFSA to re-assess the information and update its Conclusion on the ED potential of the substance in accordance with the new criteria. For this purpose, EFSA has performed an assessment of the ED properties of the active substance asulam-sodium in line with the ECHA/EFSA (2018) guidance for further consideration in the peer review.

In the context of this process, following a consultation with MSs in the Pesticide Peer Review Meeting TC 09 Mammalian toxicology – Ecotoxicology (September 2019), asulam-sodium was considered to meet the criteria for endocrine disruption for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation 2018/605. Therefore, as permitted in the mandate, the applicant was given the opportunity to submit, within a period of 3 months, additional information to address the approval criteria set out in point 3.6.5 and/or point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, and/or documentary evidence demonstrating that asulam-sodium may be used such that exposure is negligible, and/or the conditions for application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met.

Subsequently, the applicant provided further information aimed at demonstrating that the exposure of humans to asulam-sodium was negligible under realistic conditions of use. Asulam-sodium is therefore being assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009 as amended by Commission Regulation (EU) No 2018/605. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of asulam-sodium to control a serious danger to plant health. The evaluation of the relevant data is presented in the Appendices C and D to this conclusion.

A public consultation on the draft Art 4(7) scientific report, on the revised DAR on the endocrine and negligible exposure assessments made available after the 3-month clock stop (France, 2020), and on the EFSA addendum on endocrine assessment was conducted in February – April 2021. All comments received, including from the applicant and MSs, were collated in the format of a reporting table and were considered during the finalisation of the peer review.

A final consultation on the updated conclusions arising from the peer review following the mandate from the European Commission, including the negligible exposure assessment and the evaluation of the data regarding the necessity of asulam-sodium to control a serious danger to plant health which cannot be contained by other available means, took place with MSs via a written procedure in August – September 2021.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative use of asulam (variant evaluated asulam-sodium) as a herbicide on spinach and tulip, hyacinth and lily for bulb production, as proposed by the applicant. MRLs were assessed in spinach. In addition, the

[3] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

[4] ECHA and EFSA (European Chemicals Agency and European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.

conclusions were updated with regard to the ED properties following the mandate received from the European Commission in February 2019. Furthermore, this conclusion also addresses the assessment required from EFSA under Article 12 of Regulation (EC) No 396/2005, provided the active substance will be approved under Regulation (EC) No 1107/2009 without restrictions affecting the residue assessment. In the event of a non-approval of the active substance or an approval with restrictions that have an impact on the residue assessment, the MRL proposals from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required.

In addition, the peer review also provided considerations on whether exposure to humans and the environment from the representative uses of asulam-sodium can be considered negligible, taking into account the European Commission's draft guidance on this topic. An evaluation of data concerning the necessity of asulam-sodium as a herbicide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented (see Appendices C and D).

A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for asulam-sodium according to Annex II of Regulation (EC) No 1107/2009 are summarised in Appendix A.

A key supporting document to this updated conclusion is the peer review report (EFSA, 2021a), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the DAR;
- the reporting table (24 October 2016 and 19 May 2021[5]);
- the evaluation table (27 March 2018, updated in August-September 2021);
- the report(s) of the scientific consultation with MS experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the EFSA addendum on endocrine assessment;
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR, including its revisions (United Kingdom, 2018; France, 2020, 2021), the Peer Review Report and the EFSA addendum on endocrine assessment (EFSA, 2021b), all these documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion 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

Asulam is the ISO common name for methyl sulfanilylcarbamate (IUPAC). Asulam-sodium is the modified ISO common name for sodium [(4-aminophenyl)sulfonyl](methoxycarbonyl)azanide (IUPAC), a derivative of asulam.

The representative formulated product for the evaluation was 'Asulox', a soluble concentrate (SL) containing 438 g/L asulam-sodium (equivalent to 400 g/L asulam).

The representative uses evaluated were foliar spray applications in spinach and tulip, hyacinth and lily for bulb production to control broadleaved weeds and grass weeds. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix B.

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

[5] Reporting Table following consultation on the revised DAR on the assessment of the endocrine disrupting properties and negligible exposure assessment made available after the 3-month clock stop.

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), SANCO/825/00-rev. 8.1 (European Commission, 2010).

Asulam-sodium is produced as a technical concentrate (TK). The proposed specification is based on batch data from industrial scale production. The proposed specification range for the TK is 390–430 g/kg asulam-sodium. The minimum purity of the technical material on dry weight basis is 876 g/kg asulam-sodium, equivalent to 800 g/kg of asulam. The minimum purity is meeting the requirements of the FAO specification AGP:CP/353 (1998) for the technical material (TC) of minimum 800 g/kg asulam, equivalent to 876 g/kg asulam-sodium, developed under the old procedure. Methanol was considered relevant impurity with the maximum amount of 25 g/kg (on dry weight basis) (See Section 2).

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of asulam-sodium or the representative formulation. The main data regarding the identity of asulam-sodium and its physical and chemical properties are given in Appendix B.

Adequate methods are available for the determination of the active substance and the relevant impurity methanol in the technical material and in the representative formulation.

Residues of asulam and its metabolite malonyl-asulam in food and feed of plants origin can be determined by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with a limit of quantification (LOQ) of 0.1 mg/kg asulam plus its metabolite malonyl-asulam expressed as asulam, in all commodity groups. Data gaps were, however, identified for the revalidation of the method proposed as the monitoring method for the four crop groups using three extraction steps, and as a consequence, the corresponding update of the independent laboratory validation (ILV) for this method.

Pending on the final residue definition in food and feed of animal origin a monitoring method might be needed.

An appropriate LC–MS/MS method exists for monitoring the residues of asulam in soil with a LOQ of 0.005 mg/kg. An adequate LC–MS/MS method was available for the determination of residues of asulam and its metabolite sulfanilamide in water with a LOQ of 0.05 μg/L for each compound. Asulam residues in air can be determined by LC–MS/MS with a LOQ of 10 $\mu g/m^3$.

2. Mammalian toxicity

The toxicological profile of the active substance asulam and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 140 (April 2017), and the Peer Review Teleconferences 162a (January 2018), 09 (September 2019) and 59 (July 2021). The assessment was based on the following guidance documents: SANCO/221/2000-rev. 10-final (European Commission, 2003); SANCO/10597/2003-rev. 10.1 (European Commission, 2012; EFSA PPR Panel, 2012; EFSA, 2017; EFSA 2014; ECHA, 2015) and the available draft Technical Guidance Document on assessment of negligible exposure (European Commission, 2015).

The applicant submitted a set of valid toxicity studies on asulam or asulam-sodium according to Regulation (EC) 544/2011[6] to assess the toxicological profile of asulam. The batches used in toxicity studies were representative of the proposed technical specification for the active substance and associated impurities (see Section 1). Regarding impurities, methanol was considered a relevant impurity (maximum content 2.5%). Asulam and asulam-sodium are considered toxicologically equivalent.

In the toxicokinetic studies, asulam was extensively and rapidly absorbed. Oral absorption was estimated to be greater than 80%.

In the **acute toxicity** studies, the substance has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant but a skin sensitiser.

After repeated oral **short-term and long-term exposure**, the target organs included blood (rat, mouse), kidney and the adrenal (rat), and the thyroid (rat, dog). The relevant short-term oral no observed adverse effect level (NOAEL) is 100 mg/kg body weight (bw) per day (dog studies), whereas the relevant long-term NOAEL is 36 mg/kg bw per day (2-year rat). The applicant informed the RMS

[6] Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ 155, 11.6.2011, p. 1–66.

that a new dermal toxicity study is available but it cannot be taken into account during the peer review process (data gap**,** see Section 10).[7]

The experts discussed the **genotoxic potential** of asulam. The *in vivo* micronucleus test gave ambiguous results. The study was performed using the intraperitoneal (i.p.) route and at a higher dose level than the limit dose recommended according to the OECD guideline. The applicant submitted an additional Ames test and chromosome aberration tests with asulam and they were both negative. Asulam and asulam-sodium are considered equivalent and unlikely to be genotoxic. The new *in vitro* chromosome aberration test can be considered acceptable and showed negative[8] results. In the previous *in vitro* chromosome aberration test, some concerns were raised on the acceptability of the test. It was also noted that the positive response in one of the *in vitro* mouse lymphoma assays (MLA) was observed at a higher dose level than the top dose level recommended in the gene mutation assay. All the experts agreed that no concerns are present regarding the *in vitro* data. Some experts indicated that a new *in vivo* test should be requested considering also that chronic and carcinogenicity studies in rats showed limitations (high mortality). Some experts expressed the opinion that a new *in vivo* micronucleus test should be performed using the oral route at the limit dose of 2,000 mg/kg bw. A slight majority of experts agreed with RMS that no further studies should be required, while two experts disagreed and considered that an additional *in vivo* test should be performed. During the peer review, the applicant informed the RMS that three additional *in vitro* studies (mouse lymphoma and human lymphocytes micronucleus) with asulam-sodium technical or asulam technical were available (data gap, see Section 10) but were not eligible for the peer review. Overall, a slight majority of experts agreed that based on the weight of evidence asulam and asulam-sodium are unlikely to be genotoxic.

The substance showed no **carcinogenic potential** in rats and mice. With regard to **reproductive toxicity**, no effects were observed in the offspring, whereas a reduced litter size was observed in the first generation in the absence of maternal toxicity. As a consequence, the parental NOAEL of 224 mg/kg bw per day and the reproductive NOAEL of 46 mg/kg bw per day was agreed. With regard to fetal development, no teratogenic effect was observed but only a delayed/reduced ossification in the rat fetuses at 2,000 mg/kg bw per day.

In rats, mice and dogs, repeated dose studies did not show any evidence of cholinesterase inhibition and no further **neurotoxicity** studies were required.

The agreed acceptable daily intake (**ADI**) is 0.36 mg/kg bw per day based on the 2-year rat study, the acceptable operator exposure level (**AOEL**) is 0.46 mg/kg bw per day based on the rat multigeneration study and the acute reference dose (**ARfD**) is 1.0 mg/kg bw based on the 12-month dog study. All reference values were derived applying an uncertainty factor of 100, and no correction was made for oral absorption when setting the AOEL. In the context of negligible exposure assessment, the acute AOEL (**AAOEL**) was set at 1 mg/kg bw, on the same basis as the ARfD.

The standard **non-dietary exposure** assessment was performed with dermal absorption values established on the basis of the EFSA guidance 2012, and the resulting operator, worker, bystander and resident exposure estimates were below the AOEL without the use of personal protective equipment by operators (German Model and UK POEM) and workers (EUROPOEM). For the **negligible non-dietary exposure** assessment, the dermal absorption values of 10% for the concentrate and 14% for the dilution were calculated on the basis of a new *in vitro* study with human skin, and according to the EFSA guidance 2017. Considering the first tier according to the available draft guidance (European Commission, 2015), the **operator** exposure estimates for the two representative uses (only pre-emergence use on spinach, and pre-/post-emergence use on flower bulbs) are below 10% of the AOEL with the use of PPE (gloves), and below 10% of the AAOEL with additional PPE (gloves, hood and visor). The exposure estimates for **workers** exceed 10% of the AOEL for the use on flower bulbs (covered by re-entry on bulb vegetables in the EFSA calculator), and are below 10% of the AOEL for the use on spinach (pre-emergent, covered by re-entry on bare soil in the EFSA calculator). The exposure estimates for **bystander** children are below 10% of the AAOEL if a buffer strip of 5 m is ensured, or if drift reduction is applied during tractor-mounted application. For the **residential** children, the exposure estimates are above 10% of the AOEL even with drift reduction and a buffer strip of 10 m. It is noted that further refinement of worker and residential children exposure could be provided by experimentally determined dislodgeable foliar residue (DFR) values for the post-emergence use on flower bulbs.

[7] It is noted that the RMS assessed the new studies and considered that they did not show adverse data.

[8] This study was not available to ECHA RAC (2016). It is noted that ECHA RAC (2016) considered that the available data are inconclusive and that it was therefore not possible to classify asulam-sodium for germ cell mutagenicity according to the CLP criteria.

As second tier assessment according to European Commission (2015), the margin of exposure between the non-dietary exposure estimates and the systemic NOAEL for thyroid effect (i.e. 36 mg/kg bw per day, see also Section 6 below) is above 1,000 for operators using PPE (gloves), for workers re-entering spinach, and for bystander/resident adults. For workers re-entering flower bulbs and for bystander/resident children, the margin of exposure is below 1,000.

It is noted that two MSs disagreed with the approach of negligible exposure according to the draft Technical Guidance (European Commission, 2015) and support the use of real exposure studies, if available, to demonstrate that exposure values are below the limit of quantitation to fulfil the criteria of negligible exposure.

The toxicological profile of the **metabolite** sulfanilamide appears to be qualitatively similar to asulam. Quantitatively it appears of higher toxicity than asulam. However, it is not possible to properly estimate differences on potency between the compounds and specific reference values were set. The majority of experts agreed to set a specific ADI of 0.005 mg/kg bw per day based on the NOAEL of 30 mg/kg bw per day (uncertainty factor (UF) of 6,000 to take into account exposure duration and lack of reproductive toxicity studies). One MS and the RMS disagreed. The experts at the meeting did not discuss the ARfD. EFSA recommends to follow the same approach as discussed during the meeting for the ADI, i.e. considering the lack of reproductive toxicity studies, the resulting ARfD would be 0.03 mg/kg bw (NOAEL of 30 mg/kg bw per day in 28-day study, UF of 1,000 to take into account the lack of reproductive toxicity studies), as reflected by the RMS revisions made post Experts' meetings. The experts agreed that reference values of asulam also apply to metabolites malonyl-asulam, acetyl asulam, formyl asulam, asulam glucoside and desamino asulam. The experts agreed that reference values of sulfanilamide also apply to metabolites malonyl sulfanilamide, 4-acetylbenzene sulfonamide, sulfanilic acid and acetyl sulfanilamide. No conclusion could be drawn regarding asulam dimers 1 and 2 since the precise structure is unknown.

3. Residues

Asulam was discussed at the Pesticide Peer Review experts' meeting 158 and Peer Review Teleconference 162b.

The assessment in the residue section is based on the guidance documents listed in the document 1607/VI/97 rev.2 (European Commission, 1999), the European Commission guideline document on MRL setting (European Commission, 2011), the JMPR recommendations on livestock burden calculations (JMPR, 2004, 2007) and OECD publication on MRL calculations (OECD, 2011).

Metabolism was investigated in spinach following soil application (pre-emergence) and foliar application (post-emergence), and in ryegrass upon foliar application.

In spinach, asulam and malonyl asulam were found to be the predominant compounds of the total residues following pre-emergence (45–56% total radioactive residue (TRR)) and post-emergence (73.6–96.4% TRR) applications. Other compounds occurred at lower proportions (asulam glucoside 26% TRR, acetyl asulam 8% TRR and desamino asulam 14% of TRR). Acetyl sulfanilamide was found in the pre-emergence spinach samples and was recovered together with sulfanilamide in the spinach residue field trials at short preharvest intervals (PHIs) (up to 7 days). The study on rye grass showed a steady decrease of the proportion of free asulam over the course of time (from initially 60% TRR to 22% TRR) coupled with an increase of proportions of its hexose/pentose conjugates. Acetyl asulam and desamino asulam occurred at 17% and 14% TRR, respectively.

As for the higher potency of sulfanilamide compared to asulam (see Section 2), sulfanilamide is a relevant metabolite. The reference values of sulfanilamide cover also acetyl sulfanilamide and malonyl sulfanilamide.

On basis of the available data and information, the **residue definition for risk assessment** for leafy crops was set as (1) sum of asulam, malonyl asulam and sugar conjugates of asulam expressed as asulam and (2) sulfanilamide, to be considered separately. For **monitoring**, the residue definition is proposed as sum of asulam and malonyl asulam expressed as asulam. The metabolism data on ryegrass was not considered sufficient to fully address metabolism for the cereals/grass crop category as residues in cereal grains were not investigated.

Due to flaws in the available study, the assessment of residues in rotational crops and the residue definition could not be concluded; therefore, a data gap (see Section 9.1) was identified for a rotational crop metabolism study to be conducted in compliance with current recommendations. When appropriately designed, such a study should cover the issue of soil unextractable residues, as discussed in Section 4. The available study indicated significant total residue levels in all edible parts of

the tested rotational crops (spinach, wheat and radish) at all tested plant-back intervals up to 1 year following the use of asulam. Therefore, in view of significant residue levels but the lack of proper identification and quantification of the individual residue components in rotational crops, it cannot be concluded that the provisions of negligible exposure according to Regulation (EC) 1107/2009 are met. For all representative uses assessed, including the uses in spinach for seed cultivation and flower bulb production, rotation with crops used as food and feed items is common practice. Specific plant-back restrictions were not proposed as part of the GAPs for the different uses and therefore it could not be assessed if such restrictions would have been effective to avoid residues in rotational crops (see also reporting table points 83 and 85 in EFSA 2021a).

A study simulating industrial and household food processing demonstrated that asulam degrades with significant formation of sulfanilamide under all of the representative conditions (23% applied radioactivity (AR) at pasteurisation, 62% at baking/boiling and 49% at sterilisation) and that malonyl asulam degrades into malonyl sulfanilamide (7%, 26% and 27%, respectively). Taking into account in addition to the higher relative toxicity of sulfanilamide and malonyl sulfanilamide, the residue definition for risk assessment for processed commodities is set as (1) sum of asulam, malonyl asulam and sugar conjugates of asulam expressed as asulam and (2) sum of sulfanilamide and malonyl-sulfanilamide expressed as sulfanilamide. The residue definition for monitoring is proposed as sum of asulam and malonyl-asulam expressed as asulam.

With regard to the primary crop spinach, a livestock assessment is not triggered. Whether livestock exposure would be significant in terms of relevant metabolite residues in rotational crops cannot be concluded due to a data gap (see Section 9.1). It remains therefore open whether the available livestock metabolism studies in goat and hen are fully appropriate to address the residue situation with regard to residues in feed items. The animal studies were conducted only with asulam and it cannot be excluded that additional metabolites, not covered by the available studies, may become main drivers for livestock exposure. The residue definitions in animal commodities were therefore derived on a tentative basis for risk assessment as (1) asulam and (2) acetyl sulfanilamide expressed as sulfanilamide and for monitoring as asulam.

A sufficient number of valid residue trials support the critical GAP (cGAP) in spinach (northern Europe (NEU), post-emergence application) and permit derivation of input values for monitoring/MRL setting. The highly variable residues in spinach across the range of residues trials are noted, and residues were generally above the LOQ. However, the number of trials for consumer dietary exposure assessment in line with the residue definitions for risk assessment and at the requested PHI is only four, and on this basis, a median conversion factor was derived and applied to complete the risk assessment. In addition, two processing trials with spinach out of four were considered appropriate to derive processing yield factors taking account of the formation of residues of higher toxicity during processing. As these processing factors are not considered very robust, and in order to refine the risk assessment further, an additional processing residue trial is required (data gap, see Section 9.1).

To confirm integrity of residues until final analysis of all samples in the residue field trials and processing trials, information on the volatility and reactivity of sulfanilamide, malonyl sulfanilamide and acetyl sulfanilamide is required (data gap, see Section 9.1).

Two separate consumer risk assessments were conducted for the sum of asulam, malonyl asulam and sugar conjugates of asulam expressed as asulam, and for the sum of sulfanilamide and malonyl-sulfanilamide expressed as sulfanilamide, taking account of the formation of residues of higher potency during food processing.

For the sum of asulam, malonyl asulam and sugar conjugates of asulam expressed as asulam the theoretical maximum daily intake (TMDI), calculated with the MRL reaches a maximum of 5.9% of the ADI of 0.36 mg/kg bw per day. The international estimated short-term intake (IESTI) reaches a maximum of 54% of the ARfD of 1.0 mg/kg bw for fresh spinach, and 32.5% of the ARfD for processed spinach.

For the sum of sulfanilamide and malonyl-sulfanilamide expressed as sulfanilamide, the international estimated daily intake (IEDI) was less than 1% of the ADI of 0.005 mg/kg bw per day, and the IESTI reaches a maximum of 94.2% of the ARfD 0.03 mg/kg bw for processed spinach. The assessment for sulfanilamide and related residues is provisional and surrounded by high uncertainty due to limitations in the derivation of robust processing yield factors from the available processing studies. The assessment may overestimate actual consumer exposure to sulfanilamide and related residues from processed spinach, but the degree of overestimation is currently unknown. The assumptions on which the calculation has been based should be verified by additional data in processed spinach commodities, specifically by investigating the role of asulam glucosides (much higher levels than free asulam in the

raw agricultural commodities (RAC)) in the formation of sulfanilamide related residues, which is not addressed by the current submission. Moreover, validation of the residue levels in the available processing trials by information on storage stability is required. It is also noted that potential residues in rotational crops have not been considered due to insufficient data to conclude the assessment in this area, and these residues could be related to the major soil metabolite sulfanilamide (see Section 4).

EFSA reminds that the separated assessment approach is disregarding the common effects of asulam and sulfanilamide, and their related residues, specifically in view of the conclusion in Section 2 that the toxicological profile of asulam and sulfanilamide appears qualitatively similar but only their potency is different. Thus, considering a combined assessment without further refinement by appropriate processing data, it cannot be currently concluded whether or not intakes may exceed reference values with regard to consumption of processed spinach. Therefore, and in view of the uncertainties reported, the consumer risk assessment cannot be considered finalised for the representative use in spinach. It is noted that the RMS expressed confidence that an exceedance for combined intakes is unlikely.

Following the assessment if the provisions of negligible exposure according to Regulation (EC) 1107/2009 are met, it is concluded that uses on spinach for consumption, including pre and post emergence uses lead to residues above 0.01 mg/kg and above the LOQ of the analytical method and hence negligible dietary exposure cannot be assumed. In addition, the uses in spinach for seed cultivation and in tulip, hyacinth and lily for bulb production can involve rotation with edible crops, and consumer exposure to significant residues in rotational crops above 0.01 mg/kg and above the LOQ of the analytical method cannot be excluded based on the available information, while data to refine this assessment further are still pending.

4. Environmental fate and behaviour

The test substance used in most fate and behaviour investigations was asulam-sodium salt (where concentrations investigated were below its aqueous solubility), but some studies were conducted with asulam. In solution, asulam-sodium dissociates, with the ionised and unionised forms being in equilibrium, with the proportion of the different forms depending on the pH of the surrounding environment of the compound. In the environment other counter ions, which are present can also form salts with asulam. 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, asulam exhibited low to moderate persistence, forming the major (> 10% AR) metabolite sulfanilamide (max. 14% AR) which also exhibited low to moderate persistence. Mineralisation of the phenyl ring ^{14}C radiolabel to carbon dioxide accounted for 2.9–7.5% AR after 118–120 days. The formation of unextractable residues (not extracted by acetone/water followed by acidified water and acidified acetonitrile soxhlet reflux) for this radiolabel accounted for 63.9–76.2% AR after 118–120 days. As in some of the soils investigated mineralisation at 100 days was < 5% AR and unextractable residues were > 70% AR, the investigation for potential long-term effects from unextractable residues is triggered and needs to be addressed. This is discussed further in Sections 3 and 5. In anaerobic soil incubations asulam was essentially stable. Asulam exhibited very high to high mobility in soil. Sulfanilamide exhibited high to medium soil mobility. It was concluded that the adsorption of asulam, asulam salts and sulfanilamide was not pH dependent.

In laboratory incubations in dark aerobic natural sediment water systems, asulam exhibited medium persistence. The unextractable sediment fraction (not extracted by acetone/water or methanol) was the major sink for the phenyl ring ^{14}C radiolabel, accounting for 45–73% AR at 104–120 days. Mineralisation of this radiolabel accounted for 1.9–11% AR at 90–104 days. The rate of decline of asulam in laboratory sterile aqueous photolysis experiments was quicker than that which occurred in the aerobic sediment water incubations. The major phototransformation products identified were AP formamide (max. 24% AR, pH 9) MCAPAP carbamate (max. 12% AR, pH 9) and sulfanilic acid (max. 55% AR, pH 4). The necessary surface water and sediment exposure assessments (predicted environmental concentration (PEC) calculations) were carried out for the metabolite sulfanilamide, using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For the substance asulam and the aqueous phototransformation products, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available where the FOCUS surface water crop leafy

vegetables was used in simulations as a surrogate for spinach and flower bulbs.[9] The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 5 m being implemented for the drainage scenarios (representing a 13.5–72.9% spray drift reduction), and no-spray buffer zones up to 5 m (also 13.5–72.9% spray drift reduction) combined with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 1.1.4) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (2007) report acknowledges that for substances with KFoc < 2,000 mL/g (i.e. asulam), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (2009) scenarios and the models PEARL 4.4.4 and PELMO 4.4.3[9] for the substance asulam and its soil metabolite sulfanilamide where the FOCUS groundwater crop cabbage was used in simulations as a surrogate for spinach and flower bulbs. The potential for groundwater exposure from the representative uses by asulam and its salts and sulfanilamide above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all seven FOCUS groundwater scenarios defined for the FOCUS crop cabbage.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (see Section 9.1).

The PEC for asulam and its metabolites in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B of this conclusion. A key to the wording used to describe the persistence and mobility of the compounds assessed can be found in Appendix E.

5. Ecotoxicology

The following documents were considered for the risk assessment: European Commission (2002a,b), SETAC (2001) and EFSA (2009).

Some aspects of the risk assessment of asulam were discussed at the Pesticide Peer Review meeting 157 (April 2017).

A low acute risk to **birds and wild mammals** to asulam was concluded for both representative uses. However, the long-term risk for the representative uses to birds and mammals was indicated as high for all generic focal species at tier-1 risk assessment with the exception of small insectivorous mammals. Therefore, a number of refinement options were proposed (e.g. residue decline in plants, ecological information of selected species, data on body weight and food consumption of common voles). However, the data available for the refinement options were not considered suitable to be used in quantitative risk assessments. In addition, qualitative arguments (i.e. weight of evidence) were also provided for the risk assessments for small herbivorous mammals. The RMS did not conclude on a low risk for the representative uses of asulam, nor was it supported during the peer-review. Since the high risk identified with the tier-1 risk assessments could not be addressed, a data gap was identified for further information to address the long-term risk to birds and wild mammals (this issue is a critical area of concern). The biological relevance of the decrease in eggshell thickness and the related endpoint was discussed and confirmed by the experts at the Peer Review Experts' meeting TC 09 (September 2019). The additional information provided by the applicant during the additional stop of the clock were also further assessed. However, those were not considered to change the overall conclusion reached on the biological relevance of the observed effects on eggshell thickness.[10]

A low risk to birds and mammals via secondary poisoning and via consumption of contaminated drinking water was concluded.

As regards **aquatic organisms**, a low risk for asulam was concluded for both representative uses up to FOCUS Step 3 level for fish, aquatic invertebrates and algae. However, the risk for aquatic plants was indicated as high for the majority of the FOCUS scenarios (at FOCUS step 3). Therefore, FOCUS step 4 PEC_{sw} were calculated considering a 5-m no-spray buffer zone and 80% run-off mitigation (i.e.

[9] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.
[10] See EFSA ED assessment for further details on the additional information (Dietzen and Ludwigs, 2018) in EFSA, 2021b.

considering vegetative filter strips). The risk assessment at FOCUS step 4 indicated a low risk for all the relevant scenarios except for FOCUS R4 for the representative use on spinach (data gap, see Section 10).

A low risk to **metabolite** sulfanilamide was concluded considering the available toxicity endpoints for algae and aquatic plants for both representative uses. No toxicity data were available for the photolytic metabolites (AP formamide, MCAPAP carbamate, sulfanilic acid) with the exception of an endpoint for aquatic plants for sulfanilic acid. However, screening assessments by assuming that these metabolites are 10 times more toxic to aquatic organisms than asulam were conducted. When a risk mitigation of a 5-m no-spray buffer zone and 80% run-off mitigation was considered (i.e. FOCUS step 4), a low risk was concluded for these metabolites for both representative uses.

A low risk to **bees** was concluded on the basis of the available acute oral and acute contact toxicity endpoints for both representative uses. It is noted that no additional data for bees (e.g. chronic toxicity data) were available as no additional data is required by the regulation applicable for asulam.

Based on the available laboratory data, a low risk to **non-target arthropods** was concluded for both representative uses. Also, a low risk for asulam and for sulfanilamide was concluded for soil macro- and microorganisms for both representative uses on the basis of the available laboratory data. However, long-term studies (e.g. field studies) investigating the long-term effects of non-extractable residues were not available, although this assessment is triggered by the available fate and behaviour information (see Section 4). A data gap (see Section 9.1) was identified to address this issue.

A regards **non-target terrestrial plants**, a low risk was demonstrated by a higher tier probabilistic risk assessment and considering a risk mitigation measure a 5-m no-spray buffer zone (or any risk mitigation measure with equivalent effectivity to a 5-m no-spray buffer zone).

A low risk for **biological methods of sewage treatment** was concluded for the uses of asulam.

6. Endocrine-disrupting properties

With regard to the assessment of the endocrine-disrupting potential of asulam for humans according to the ECHA/EFSA guidance (2018), the number and type of effects induced, and the magnitude and pattern of responses observed across studies were considered to determine whether asulam interacts with the oestrogen, androgen and steroidogenesis (EAS)- and thyroid (T)-mediated pathways. Additionally, the conditions under which the effects occur were examined, in particular, whether or not endocrine-related responses occurred at dose(s) that also resulted in overt toxicity. This assessment, therefore, provides a weight-of-evidence analysis of the potential interaction of asulam with the EAS and T signalling pathways using the available evidence in the dataset.

The data set for the T-modality was considered complete. There is evidence of a T mediated pattern of adversity observed in both rat and dog studies also at doses below, or at the maximum tolerable dose (MTD). Thyroid peroxidase (TPO) inhibition was the postulated molecular initiating event and asulam induces adverse effects in the thyroid gland i.e. thyroid follicular cell hypertrophy/ hyperplasia (rat 90-day study, chronic/carcinogenicity study and dog 1-year study), thyroid epithelial cell whorls (rat carcinogenicity study) and increase in thyroid weight (rat 90-day study and dog 90-day and 1-year studies). Based on the available data set and the mode of action (MoA) analysis, it was concluded that the ED criteria for T-modality are met for asulam (Scenario 1b of the ECHA/EFSA guidance (2018) ED Guidance), leading to a critical area of concern (see Section 9.2). The lowest NOAEL for T-mediated adversity was observed in the 2-year rat study at 36 mg/kg bw per day.

EAS-mediated adversity and EAS-mediated endocrine activity have not been observed, but the EAS modalities have not been sufficiently investigated. Therefore, further data need to be generated before a conclusion on whether or not the ED criteria are met for the EAS modalities can be drawn (Scenario 2a(iii) of the ECHA/EFSA guidance (2018) ED Guidance). A ToxCast oestrogen receptor (ER) model is available and negative for asulam, therefore, there is no need to further explore the E modality. According to the EFSA/ECHA GD (2018), the following tests are needed to investigate the A and S modalities:

- A study in line with OECD Test Guideline (TG) 458 (Stably Transfected Human Androgen Receptor Activation Assay (AR STTA) assay).
- Aromatase assay (human recombinant) OPPTS 890.1200 (US EPA 2009 In: Endocrine Disruptor Screening Program Test Guidelines. Office of Prevention, Pesticides and Toxic Substances (OPPTS), US EPA, Washington (DC).
- A study in line with OECD TG 456 (H295R Steroidogenesis assay).
- A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456, OPPTS 890.1200 and OECD TG 458 are negative.

If the above tests are negative, the active substance will not meet the ED criteria for EAS modalities. However, in case of positive result/s based on the above tests for at least one modality, additional testing might be needed:

- OECD TG 443 (with the inclusion of cohort 1B) or OECD TG 416 (including additional endpoints in accordance with the EFSA (2020) technical report: 'Outcome of the pesticides peer review meeting on general recurring issues in mammalian toxicology'.

However, in the context of this assessment, since asulam is already considered as an endocrine disruptor for the T-modality, additional testing to investigate the A- and S-modalities is not needed.

The T-mediated adverse effects observed in mammals are not considered to be relevant for wild mammal populations[11] and therefore the outcome of the assessment reported above for humans does not apply to **wild mammals as non-target organisms** regarding the T-modality.

Regarding EAS modalities, the available dataset was not considered as sufficiently investigated both for **wild mammals**, in line with the conclusions for humans, and **non-mammalian species**.

In all the available studies with birds, a reduction in eggshell thickness was observed. This was considered adverse by the experts at the Peer Review Experts' meeting TC 09 (September 2019). In the suitable reproductive study with quail,[12] this effect was coupled with an increase in the number of cracked eggs and a decrease in hatchling/maximum set[13] and 14-day-old survivors/maximum set.[14] A non-EATS MoA was postulated (cyclooxygenase inhibition leading to reproductive failure) for the reduction in birds' eggs shell thickness. However, for the postulated MoA, data were only available in relation to a later key event (KE) and the adverse outcome. Therefore, the available information was insufficient to support the postulated MoA.

Overall, for non-target organisms, further data would be needed to draw a conclusion on the ED properties of asulam on non-target organisms for both T- and EAS-modalities, i.e. in the first instance a test according to OECD Test Guideline 231 (Amphibian Metamorphosis Assay) and a test according to OECD TG 229 (Fish Short-Term Reproduction Assay). Moreover, information should be generated to further substantiate the postulated non-EATS MoA, i.e. to elucidate the potential endocrine activity.

Based on the above considerations, the assessment of the ED properties of asulam for **non-target organisms** according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded, leading to an issue not finalised (see Section 9.1). However, further data were not requested taking into account that asulam was considered to meet the criteria for endocrine disruption for humans for the T-modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605.

Regarding human health, considerations on **negligible exposure** are reported in Section 2 (mammalian toxicology) and Section 3 (residues).

Regarding the environment, the available PEC for asulam in soil, surface water and sediment for all the representative uses assessed are above levels that can be routinely measured.[15] There will be exposure of asulam and its salts via food items of non-target organisms for the representative uses, as these organisms will enter fields on the same day an application is made.

[11] See section 3.1.3 of the EFSA ED assessment (EFSA, 2021b).
[12] Two 6-week studies were also available with the two standard species. However, those are not considered fully suitable for risk assessment because of the shorter exposure duration, although an increase on eggshell thinning was observed.
[13] The number of hatchlings per female divided by the largest number of eggs set from any female.
[14] The number of 14-day-old survivors per pen divided by the largest number of eggs set.
[15] In line with the ethos of FAO/WHO (2009) further discussed in EFSA Scientific Committee (2012) and limits of analytical quantification needed for monitoring methods set out in European Commission (2021).

7. 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)	Ecotoxicology
Asulam and its salts	Data gap
Sulfanilamide	Low risk to soil organisms

Table 2: Groundwater[(a)]

Compound (name and/or code)	> 0.1 µg/L at 1 m depth for the representative uses[(b)] Step 2	Biological (pesticidal) activity/ relevance Step 3a	Hazard identified Steps 3b and 3c	Consumer RA triggered Steps 4 and 5	Human health relevance
Asulam and its salts	No	Yes	Assessment not triggered	Assessment not triggered	Yes
Sulfanilamide	No	Assessment not triggered	Assessment not triggered	Assessment not triggered	Assessment not triggered

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Asulam and its salts	Low risk to aquatic organisms with risk mitigation for all, but one FOCUS scenarios (data gap for R4 FOCUS scenario)
Sulfanilamide	Low risk to aquatic organisms
Sulfanilic acid	Low risk to aquatic organisms with risk mitigation
AP formamide	Low risk to aquatic organisms with risk mitigation
MCAPAP carbamate	Low risk to aquatic organisms with risk mitigation

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

Table 4: Air

Compound (name and/or code)	Toxicology
Asulam	Low acute inhalation toxicity to rats (Rat LC_{50} inhalation > 5.46 mg/L

LC_{50}: lethal concentration, 50%.

8. Particular conditions proposed to be taken into account by risk managers

Risk mitigation measures (RMMs) identified following consideration of MS and/or applicant's proposal(s) during the peer review, if any, are presented in this section. These measures applicable for human health and/or the environment leading to a reduction of exposure levels of operators, workers, bystanders/residents, environmental compartments and/or non-target organisms for the representative uses are listed below. The list may also cover any RMMs as appropriate, leading to an acceptable level of risks for the respective non-target organisms.

It is noted that final decisions on the need of RMMs to ensure the safe use of the plant protection product containing the active substance will be taken by risk managers during the decision-making phase. Consideration of the validity and appropriateness of the RMMs remains the responsibility of MSs at product authorisation, taking into account their specific agricultural, plant health and environmental conditions at national level.

Table 5: Risk mitigation measures proposed for the representative uses assessed

Representative use	Spinach**	Tulip hyacinth and lily (bulb production)
Operator standard exposure	No RMM needed	No RMM needed
Operator negligible * exposure	Use of PPE is required(a)	Use of PPE is required(a)
Worker standard exposure	No RMM needed	No RMM needed
Worker negligible* exposure	No RMM needed	RMM insufficient
Bystander/resident standard exposure	No RMM needed	No RMM needed
Bystander/resident negligible* exposure	Buffer strip 5 m or drift reduction for bystander children; RMM insufficient for residential children	Buffer strip 5 m or drift reduction for bystander children; RMM insufficient for residential children
Risk to aquatic organisms	RMM equivalent to a 5-m no-spray buffer zone and 80% run-off mitigation should be taken into account for geoclimatic situations represented by D3, D6, R2, R3 FOCUS surface water scenarios	RMM equivalent to a 5-m no-spray buffer zone and 80% run-off mitigation should be taken into account for geoclimatic situations represented by D3, D6, R2, R3 FOCUS surface water scenarios. In addition, RMM with equivalent effectivity would be needed for the R1 scenario.
Risk to non-target terrestrial plants	RMM equivalent to RMM equivalent to a 5-m no-spray buffer zone should be taken into account	RMM equivalent to RMM equivalent to a 5-m no-spray buffer zone should be taken into account

RMM: risk mitigation measure.
*: For negligible exposure, RMMs are reflected in the table in case they would lead to exposure below or equal to 10% of the (A)AOEL. In order to give a clear overview, it is also mentioned when RMMs are not needed or are insufficient to lead to an exposure level meeting the criteria for standard or negligible exposure. For further details and considerations as regards negligible exposure assessment please refer to Section 2 and Appendix B.
**: For non-dietary exposure assessment: pre- and post-emergence use for standard exposure, and pre-emergence use only was supported for negligible exposure.
(a): For tractor-mounted applications: gloves (EFSA, 2014).

9. Concerns and related data gaps

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 one or more of 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[16] 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.

The following issues or assessments that could not be finalised have been identified, together with the reasons including the associated data gaps where relevant, which are reported directly under the specific issue to which they are related:

1) The consumer exposure assessment for sulfanilamide metabolites is highly uncertain and is leading to provisional estimates of acute consumer exposure close to the ARfD for the use in spinach. When considering the presumed qualitatively similar toxicological profile of asulam

[16] 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.

and sulfanilamide but their different potency, it cannot be currently concluded whether or not a combined assessment may result in exceedance of the acute reference values with regard to processed spinach consumption while a refined consumer risk assessment cannot be finalised (see Section 3).

a) At least one additional processing residue trial in spinach with sufficiently high initial residue levels in the RAC and analysing for all relevant compounds (malonyl asulam, malonyl sulfanilamide, free and conjugated residues of asulam and sulfanilamide), in accordance with current requirements and guidelines. With this experiment it should also be demonstrated whether sulfanilamide glucosides could be formed from asulam glucosides or whether complete hydrolysis into sulfanilamide occurs (relevant for representative uses in spinach; see Section 3).
b) Information on the volatility and reactivity of sulfanilamide, malonyl sulfanilamide and acetyl sulfanilamide in order to conclude whether storage stability data on these compounds can be omitted or are required to confirm integrity of residues until final analysis of all samples in the residue field and processing trials (relevant for representative uses in spinach; see Section 3).
c) A nature-of-residues study in rotational crops, compliant with current recommendations (relevant for all representative uses evaluated; see Section 3).
d) Satisfactory information to address the unless clause of the uniform principles 2.5.1.1 to demonstrate that under field conditions there is no accumulation in soil at such levels that unacceptable residues in succeeding crops occur was not available considering the data gap regarding the available information on the nature of residues in following crops (relevant for all representative uses evaluated; see Sections 3 and 4).

2) The consumer risk assessment from the consumption of drinking water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).

a) Satisfactory information to address the effect of water treatment processes on the nature of residues in surface water, when surface water is abstracted for drinking water was not available. Probably in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water, as well as the active substance. Should this consideration indicate that novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant for all representative uses evaluated; see Section 4).

3) The long-term risk to soil organisms from non-extractable soil residues could not be finalised (see Section 5).

a) Satisfactory information to address the long-term risk to soil organisms from non-extractable soil residues (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

4) The assessment of the ED properties of asulam for non-target organisms could not finalised for EATS and non-EATS modalities based on the available information (see Section 6).

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.

The following critical areas of concern are identified, together with any associated data gaps, where relevant, which are reported directly under the specific critical area of concern to which they are related:

5) The long-term risk to birds and wild mammals was assessed as high (see Section 5).
   a) Satisfactory information to address the long-term risk to birds and wild mammals (relevant for all representative uses evaluated; submission date proposed by the applicant: further data had already been submitted to the RMS; see Section 5).
6) Asulam is considered to meet the criteria for endocrine disruption for humans for the T-modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (see Section 6).

9.3. Overview of the concerns identified for each representative use considered (Table 6)

(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 6.)

In addition to the issues indicated below, asulam-sodium is considered to meet the criteria for endocrine disruption for humans for the T-modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605, while the assessment of the ED properties for non-target organisms according to the scientific criteria for the determination of ED properties as set out in point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, could not be finalised. For the considerations as regards negligible exposure assessment please refer to Sections 2, 3, 6, Table 5 and Appendix B.

Table 6: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		**Spinach**	**Tulip hyacinth and lily (bulb production)**
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Resident/bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[1,2]	X[2]
Risk to wild non-target terrestrial vertebrates	Risk identified	X[5]	X[5]
	Assessment not finalised		
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised	X[3]	X[3]
Risk to aquatic organisms	Risk identified	1/7 FOCUS scenarios	
	Assessment not finalised		

Representative use		Spinach	Tulip hyacinth and lily (bulb production)
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		

The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–7 for further information.

(a): It should be noted that the classification proposed in the context of this evaluation procedure under Regulation (EC) No 1107/2009 concurs with the harmonised classification and labelling in accordance with Regulation (EC) No 1272/2008.

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

10. List of other outstanding issues

Remaining data gaps not leading to critical areas of concern or issues not finalised but considered necessary to comply with the data requirements, and which are relevant for some or all of the representative uses assessed at EU level. Although not critical, these data gaps may lead to uncertainties in the assessment and are considered relevant.

These data gaps refer only to the representative uses assessed and are listed in the order of the sections:

- Revalidation of the method proposed as the monitoring method for the four crop groups using three extraction steps (relevant for all representative uses evaluated; see Section 1).
- Revalidation of the ILV for the monitoring method for plants (relevant for all representative uses evaluated; see Section 1).
- Toxicity studies submitted to United States Environmental Protection Agency (US EPA) including genotoxicity and dermal toxicity studies (relevant for all representative uses evaluated; see Section 2).
- Satisfactory information to address the unless clause of the uniform principles 2.5.1.1 to demonstrate that under field conditions there is no accumulation in soil at such levels that unacceptable impact on the environment would not occur, was not available (relevant for all representative uses evaluated; see Section 4).
- Satisfactory information to address the risk to aquatic organisms for geoclimatic situations represented by R4 FOCUS surface water scenario (relevant for the representative use on spinach; see Section 5).

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Abbreviations

ADI	acceptable daily intake
AAOEL	acute acceptable operator exposure level
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
CAS	Chemical Abstracts Service
DAR	draft assessment report
DFR	dislodgeable foliar residue
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community

EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
InChiKey	International Chemical Identifier Key
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	Intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC–MS	liquid chromatography–mass spectrometry
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOQ	limit of quantification
mm	millimetre (also used for mean measured concentrations)
MOA	mode of action
MRL	maximum residue level
MS	Member state
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
OM	organic matter content
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PHI	preharvest interval
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
RAC	regulatory acceptable concentration
SC	suspension concentrate
SFO	single first-order
SMILES	simplified molecular-input line-entry system
TK	technical concentrate
TMDI	theoretical maximum daily intake
ToxCAST	(US EPA) Toxicity Forecaster
TPO	Thyroid peroxidase
TRR	total radioactive residue
UF	uncertainty factor
WHO	World Health Organization

Appendix A – Consideration of cut-off criteria for asulam-sodium according to Annex II of Regulation (EC) No 1107/2009 of the European Parliament and of the Council

Properties		Conclusion[(a)]
CMR	**Carcinogenicity (C)**	Asulam is not considered to be carcinogenic, mutagenic (genotoxic) or toxic for reproduction according to points 3.6.2, 3.6.3, 3.6.4 of Annex II of Regulation (EC) 1107/2009.
	Mutagenicity (M)	
	Toxic for Reproduction (R)	
Endocrine-disrupting properties		Asulam is considered to meet the criteria for endocrine disruption for humans for the T modality according to point 3.6.5 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (see Section 6). The assessment of the endocrine disrupting properties of asulam for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded (see Section 6).
POP	**Persistence**	Asulam is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Asulam is not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Asulam is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	

(a): Origin of data to be included where applicable (e.g. EFSA, ECHA RAC, Regulation).

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

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6921

Appendix C – Evaluation of data concerning the necessity of asulam-sodium as herbicide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods

Appendix C can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6921

Appendix D – Data collection set

Validated Excel files submitted by MS (Belgium, 2020; Germany, 2020; the Netherlands, 2020; Denmark, 2020) and evaluated by EFSA.

Appendix D can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2021.6921

Appendix E – Wording EFSA used in section 4 of this conclusion, in relation to DT and K_{oc} 'classes' exhibited by each compound assessed

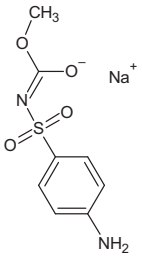
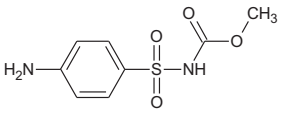
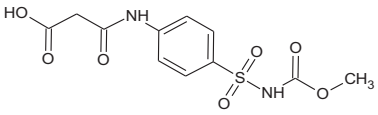
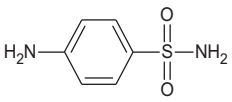
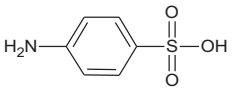
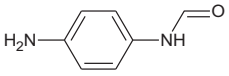
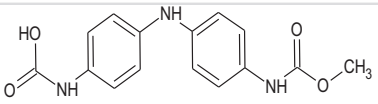
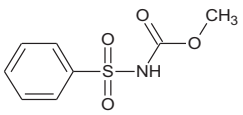
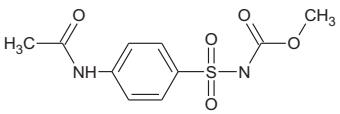
Wording	DT_{50} normalised to 20°C for laboratory incubations[(a)] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT_{50} when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1–< 10 days
Moderate persistence	10–< 60 days
Medium persistence	60–< 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

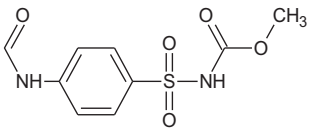
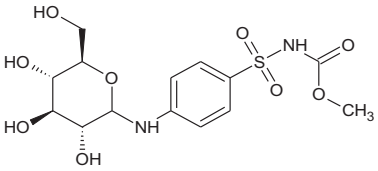
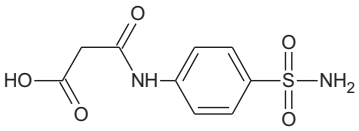
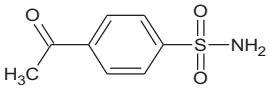
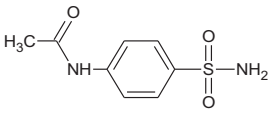
DT_{50}: period required for 50% dissipation (define method of estimation); DT_{90}: period required for 90% dissipation (define method of estimation); SFO: single first-order.
Note: These classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.
(a): For laboratory soil incubations, normalisation was also to field capacity soil moisture (pF2/10 kPa). For laboratory sediment water system incubations, the whole system DT values were used.

Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2,000
Slight mobility	2,001–5,000
Immobile	> 5,000

K_{Foc}: Freundlich organic carbon adsorption coefficient; K_{doc}: organic carbon linear adsorption coefficient.
Based on McCall et al. (1980).

Appendix F – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
asulam-sodium	sodium [(4-aminophenyl)sulfonyl](methoxycarbonyl) azanide [Na+].Nc1ccc(cc1)S(=O)(=O)/N=C(\[O-])OC PEXLHWBDBQUUOG-UHFFFAOYSA-M	
asulam	methyl sulfanilylcarbamate Nc1ccc(cc1)S(=O)(=O)NC(=O)OC VGPYEHKOIGNJKV-UHFFFAOYSA-N	
malonyl-asulam	3-{4-[(methoxycarbonyl)sulfamoyl]anilino}-3-oxopropanoic acid O=S(=O)(NC(=O)OC)c1ccc(NC(=O)CC(=O)O)cc1 OMIVAOOCWPYRFZ-UHFFFAOYSA-N	
sulfanilamide	4-aminobenzene-1-sulfonamide Nc1ccc(cc1)S(=O)(N)=O FDDDEECHVMSUSB-UHFFFAOYSA-N	
sulfanilic acid	4-aminobenzene-1-sulfonic acid Nc1ccc(cc1)S(O)(=O)=O HVBSAKJJOYLTQU-UHFFFAOYSA-N	
AP formamide	*N*-(4-aminophenyl)formamide O=CNc1ccc(N)cc1 MUQQKIMNQFFGRV-UHFFFAOYSA-N	
MCAPAP carbamate	(4-{4-[(methoxycarbonyl)amino]anilino}phenyl) carbamic acid O=C(O)Nc1ccc(cc1)Nc2ccc(NC(=O)OC)cc2 POCFWHODYFFNBX-UHFFFAOYSA-N	
MBSC desamino asulam	methyl (benzenesulfonyl)carbamate O=S(=O)(NC(=O)OC)c1ccccc1 QHSZICITQBPJNK-UHFFFAOYSA-N	
acetyl asulam	methyl (4-acetamidobenzene-1-sulfonyl)carbamate O=S(=O)(NC(=O)OC)c1ccc(NC(C)=O)cc1 WYSQQGOTBXOTIB-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
formyl asulam	methyl (4-formamidobenzene-1-sulfonyl)carbamate O=S(=O)(NC(=O)OC)c1ccc(NC=O)cc1 CEUARWBYSFKKKU-UHFFFAOYSA-N	
asulam glucoside	*N*-{4-[(methoxycarbonyl)sulfamoyl]phenyl}-D-glucopyranosylamine O=C(OC)NS(=O)(=O)c1ccc(cc1)NC2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O UQKKMJPSQNYRBO-HENWMNBSSA-N	
malonyl sulfanilamide	3-oxo-3-(4-sulfamoylanilino)propanoic acid O=S(N)(=O)c1ccc(NC(=O)CC(=O)O)cc1 GZLKRIRYRXOWCY-UHFFFAOYSA-N	
4-acetylbenzene sulfonamide	4-acetylbenzene-1-sulfonamide O=S(N)(=O)c1ccc(cc1)C(C)=O CSATVXJBGFVJES-UHFFFAOYSA-N	
acetyl sulfanilamide	*N*-(4-sulfamoylphenyl)acetamide O=S(N)(=O)c1ccc(NC(C)=O)cc1 PKOFBDHYTMYVGJ-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2018.2.2 ACD/Labs 2018 Release (File version N50E41, Build 103230, 21 July 2018).
(c): ACD/ChemSketch 2018.2.2 ACD/Labs 2018 Release (File version C60H41, Build 106041, 7 December 2018).