CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment of the active substance dimethyl disulfide

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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 France for the pesticide active substance dimethyl disulfide 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 uses of dimethyl disulfide as a nematicide, fungicide and herbicide on carrot (field use) and on tomato (greenhouse application). The reliable endpoints, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: dimethyl disulfide, peer review, risk assessment, pesticide, nematicide, fungicide, herbicide

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Summary

Dimethyl disulfide is a new active substance for which, in accordance with Article 7 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council, the rapporteur Member State (RMS), France, received an application from Arkema France on 21 December 2012 for approval. 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 15 February 2013.

An initial evaluation of the dossier on dimethyl disulfide was provided by the RMS in the draft assessment report (DAR) and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 12 of Regulation (EC) No 1107/2009. The following conclusions are derived.

The uses of dimethyl disulfide according to the representative uses proposed at the European Union (EU) level result in sufficient efficacy as nematicide, fungicide and herbicide against the target nematodes, fungi and weeds.

In the area of identity, physical chemical properties and analytical methods data gaps were identified for a confirmatory method for dimethyl disulfide in surface water and ground water, for an analytical method for determination of metabolite methanesulfonic acid (MSA) in drinking water, monitoring methods for the determination of MSA, sulfur dioxide (SO_2) and metabolite formaldehyde (HCHO) in the air.

Data gaps leading to issues that cannot be finalised were identified in the area of mammalian toxicology. In addition, a data gap to address immunotoxicity is also identified. Toxicological reference values for consumer risk assessment cannot be derived for dimethyl disulfide due to lack of testing of dimethyl disulfide by the oral route and for the metabolite MSA because the genotoxicity potential cannot be concluded. Additional exposure data are lacking for the finalisation of the risk assessment for dimethyl disulfide and HCHO in some non-dietary exposure scenarios and for all scenarios for the major air metabolites MSA and SO_2. No data were provided that are relevant for the northern countries uses. Overall, it is not possible to identify a single acceptable exposure scenario or safe condition of use for all categories of exposed populations for both 'Paladin' and 'Paladin EC' and this represents a critical area of concern.

In the residue section, data gaps were identified for additional Good Agricultural Practice (GAP)-compliant residue trials for the determination of dimethyl disulfide residues in carrots and tomatoes, supported by acceptable storage stability data and validated analytical methods for dimethyl disulfide, and for additional storage stability data on MSA, covering the maximum storage time interval of the samples of the residue trials on carrots and tomatoes. The consumer risk assessment through dietary intake and drinking water currently cannot be finalised due to the outstanding data on dimethyl disulfide and MSA.

With respect to fate and behaviour in the environment, the reliability of dissipation and degradation kinetic parameters, obtained for dimethyl disulfide in laboratory studies, is compromised by the high volatility observed in the laboratory system and the incomplete characterisation of the volatilised radioactivity. Several data gaps have been identified for the fate and behaviour section. A set of four environmental exposure calculations for each use was produced to account for the various uncertainties identified with respect of the fate and behaviour of dimethyl disulfide. Groundwater contamination by dimethyl disulfide and MSA at levels above the parametric drinking water limit of 0.1 μg/L cannot be excluded, due to the lack of reliable degradation parameter information in soil (as discussed above) as well as other uncertainties. Reliable degradation parameters being essential for modelling groundwater exposure with the usual uncertainty. A critical area of concern has been identified with respect to potential groundwater contamination by dimethyl disulfide. The relevance assessment of metabolite MSA remains open, leading to an assessment not finalised. The groundwater exposure assessment for the anaerobic soil metabolite methanethiol (MT) was also identified as an assessment not finalised. The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. This has led to the identification of a data gap and results in the consumer risk assessment not being finalised.

In the area of ecotoxicology, multiple data gaps were identified for birds and mammals, aquatic organisms, honeybees, non-target arthropods, soil organisms, endocrine-disrupting properties of dimethyl disulfide and effect on activated sludge. In addition, a data gap for a proper assessment of the off-field environment due to redeposition of dimethyl disulfide was identified. The risk assessment could not be finalised for birds and mammals (long-term dietary risk and risk from inhalation), aquatic

organisms (chronic risk), honeybees (risk for exposure via inhalation), non-target arthropods, soil macroorganisms and as regards endocrine-disrupting properties. Furthermore, critical areas of concern have been identified for birds and mammals (acute risk), aquatic organisms (acute risk) and earthworms.

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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 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).

Dimethyl disulfide is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, France (hereinafter referred to as the 'RMS'), received an application from Arkema France on 21 December 2012 for approval. 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 15 February 2013.

The RMS provided its initial evaluation of the dossier on dimethyl disulfide in the DAR, which was received by EFSA on 30 March 2018 (France, 2018). Since the dossier was submitted before the new data requirements entered into force on 1 January 2014, the DAR has been prepared by the RMS following the old data requirements in accordance with Commission Regulations (EC) No 544/2011[2] and 545/2011[3].

The peer review was initiated on 18 April 2018 by dispatching the DAR for consultation of the Member States and the applicant, Arkema France, 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 and the RMS on 1 October 2018. 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, environmental fate and behaviour and ecotoxicology.

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

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

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether dimethyl disulfide can be expected to meet the approval criteria provided for in Article 4 of the Regulation, taking into consideration recital (10) of the Regulation. A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in July - August 2019.

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 uses of dimethyl disulfide as a nematicide, fungicide and herbicide on carrot (field use) and tomato (greenhouse

[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] 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 L 155, 11.6.2011, p. 1–66.

[3] Commission Regulation (EU) No 545/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for plant protection products. OJ L 155, 11.6.2011, p. 67–126.

application) as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the DAR and considered during the peer review are presented in the conclusion. 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 maximum residue level (MRL) proposals/Annex IV proposal, if any, from this conclusion might no longer be relevant and a new assessment under Article 12 of Regulation (EC) No 396/2005 will be required. A list of the relevant end points for the active substance and the formulation is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2019), 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 (1 October 2018);
- the evaluation table (26 August 2019);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the DAR including its revisions (France, 2019) and the peer review report, both documents are considered as background documents to this conclusion.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Dimethyl disulfide is the common name for dimethyl disulfide (IUPAC). This substance is considered by the International Organization for Standardization not to require a common name.

The representative formulated products for the evaluation were 'Paladin (Atomal 12)', a liquid to be applied undiluted (AL) containing 978 g/kg dimethyl disulfide and 'Paladin EC (Atomal 13)', an emulsifiable concentrate (EC) containing 929 g/kg dimethyl disulfide.

The representative uses evaluated as a nematicide, fungicide and herbicide were shank injection to a depth of 20 cm in soil covered by a barrier film, against nematodes and various weed species in carrot (before sowing/planting) and application by drip irrigation with a barrier film, to control nematodes, fungi and weeds in protected tomato in the EU. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

It is noted that the additional uses proposed as representative in the original dossier strawberries (F) and tomatoes (G) with a higher application rate (600 kg/ha) have not been assessed and have been withdrawn by the applicant.

Data were submitted to conclude that the uses of dimethyl disulfide according to the representative uses proposed at EU level result in sufficient efficacy as a nematicide, fungicide and herbicide against the target nematodes, fungi and weeds following the guidance document SANCO/10054/2013-rev. 3 (European Commission, 2013).

A data gap has been identified for a search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, including methanesulfonic acid (MSA), dealing with side effects on health, the environment and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011). Data gap relevant for Sections 2, 3, 4 and 5.

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: European Commission, 2000a,b, 2010.

The proposed specification for dimethyl disulfide is based on batch data from industrial scale production. The proposed minimum purity of the technical material is 980 g/kg. Methanethiol (methyl mercaptan) is considered as a relevant impurity with maximum limit of 0.5 g/kg. A FAO specification is not available for the active substance.

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 dimethyl disulfide or the representative formulations. The main data regarding the identity of dimethyl disulfide and its physical and chemical properties are given in Appendix A.

Methods of analysis are available for the determination of the active substance in the technical material and formulations. Appropriate methods are available for the quantification of the relevant impurities in the technical material and the representative formulations.

Pending on the final residue definition for monitoring in food and feed of plant and animal origin, analytical methods might be required (see Section 3). It should be noted, however that analytical methods using liquid chromatography with tandem mass spectrometry (LC–MS/MS) and a confirmatory method using gas chromatography with mass spectrometry (GC–MS) for the determination of dimethyl disulfide in high water and high acid content commodities exist with a limit of quantification (LOQ) of 0.01 mg/kg.

The residue definition for monitoring in soil and surface water was defined as dimethyl disulfide, while in ground water as dimethyl disulfide and MSA. The GC–MS method exists for the determination of dimethyl disulfide in soil, while residues of MSA can be determined by LC–MS/MS with a LOQ of 0.05 mg/kg for both substances. Residues of dimethyl disulfide in surface water and ground water can be determined by GC–MS with a LOQ of 0.1 μg/L; however, a data gap was identified for a confirmatory method. A data gap was also identified for an analytical method for determination of MSA in drinking water.

The residue definition for monitoring in air was defined as dimethyl disulfide, MSA, sulfur dioxide (SO_2) and formaldehyde (HCHO). Dimethyl disulfide can be monitored in the air by GC–MS with a limit of quantification (LOQ) of 0.1 $\mu g/m^3$.

A data gap was identified for methods for the determination of the other components of the residue definition in air: MSA, SO_2 and HCHO.

Residues of dimethyl disulfide in body fluids and tissues can be determined by headspace gas chromatography with mass spectroscopy with LOQs of 0.1 mg/kg for body tissues and 0.05 mg/L for body fluids, respectively. Dimethyl sulfone ($DMSO_2$) was considered as a suitable marker for monitoring in body fluids; however, no monitoring method is available and a data gap would have been identified under the new data requirements in accordance with Commission Regulation (EU) No 283/2013[4] (see also Section 2).

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: European Commission, 2003, 2012 and ECHA/EFSA (2018).

Dimethyl disulfide was discussed at the Pesticides Peer Review Experts' Meeting 1 in April 2019.

Characterisation of the technical specification was supported through the evaluation of the composition of the batches used in the toxicology studies and through the *in silico*, i.e. QSAR, evaluation of the impurities quoted in the proposed technical specification. The non-toxicological relevance of the individual impurities was considered addressed. Methanethiol (methyl mercaptan) is considered as a relevant impurity for which, however, no concern is raised at the level indicated in the technical specification (0.5 g/kg). The analytical methods used in the toxicological studies were considered fit-for-purpose for the most relevant studies.

[4] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 93, 3.4.2013, p. 1–84.

No *in vivo* toxicokinetic study is available for dimethyl disulfide. However, as dimethyl disulfide is used as a flavouring agent, an evaluation of absorption, metabolism, distribution and elimination (ADME) was retrieved from the WHO Food Additives Series No 59 (Williams GM & Bend J, 2000 in WHO, 2008). Based on its physical-chemical properties (low molecular weight and sufficient lipophilicity), dimethyl disulfide is expected to be absorbed, not accumulated in the body and excreted mainly through the urinary tract as cysteine disulfide. Reduction is also expected to be extensive, resulting in low relative molecular mass, which would be further metabolised by various pathways. In addition, an *in vitro* study conducted in rat hepatocytes was performed, showing that dimethyl disulfide is rapidly metabolised after incubation for up to 4 h with formation of both dimethyl sulfide (DMS) and methanethiol (methyl mercaptan). $DMSO_2$, the ultimate metabolite of dimethyl disulfide, is considered as a suitable marker for monitoring in body fluids; however, no monitoring method is available (see data gap in Section 1). The available information was considered sufficient for the ADME characterisation.

Dimethyl disulfide was tested for acute toxicity in a series of oral, dermal and inhalation toxicity tests in rat: it was confirmed that the substance is toxic if swallowed and if inhaled (Acute tox. 3 – H301 and Acute tox.3 – H331)[5] but no classification is triggered for dermal exposure. Dimethyl disulfide is an eye irritant (Eye irrit. 2 – H319)[5] and causes damage to upper respiratory tract (STOT SE 1 H370)[5] with a no observed adverse effect concentration (NOAEC) for the 24-h whole-body exposure of 9 ppm, corresponding to 34.7 mg/m^3. Finally, it is a skin sensitiser in a local lymph node assay (LLNA) assay (Skin. Sens. 1 (H317))[5].

Dimethyl disulfide was tested in a series of 90-day rat inhalation studies and in a 28-day rabbit dermal toxicity study. No oral toxicity studies are available for dimethyl disulfide and no short-term inhalation toxicity studies are available in non-rodent species. From the inhalation studies, a NOAEC cannot be derived and a lowest observable adverse effect concentration (LOAEC) for local contact (nasal) irritation and a LOAEC for systemic toxicity (decreased body weight gain and clinical chemistry changes) was set at 10 ppm. Nasal changes were reversible at the LOAEC but were still persistent after a period of treatment withdrawal at the top dose of 50 ppm. After dermal exposure in rabbit for 28-day, a systemic no observed adverse effect level (NOAEL) was set at 106.3 mg/kg body weight per day with mortality observed at 1,063 mg/kg/body weight (bw) per day, whereas the local lowest observable adverse effect level (LOAEL) was set at 10.63 mg/kg/bw per day due to a persistent severe skin irritation. Moreover, due to transient narcotic effects observed in this study, as well as in other acute and repeated-dose toxicity studies, dimethyl disulfide would meet criteria for classification as STOT SE 3; H336.

The lack of testing in a second non-rodent species was considered in the definition of additional interspecies related uncertainty factors for setting the reference values by inhalation.

The potential of dimethyl disulfide to induce genotoxicity effects was assessed in several *in vitro* and *in vivo* genotoxicity assays. Overall, dimethyl disulfide is considered as devoid of *in vivo* genotoxicity.

Long-term toxicity or carcinogenicity studies with dimethyl disulfide are not available. The experts however agreed that a carcinogenic potential cannot be excluded for dimethyl disulfide, also considering the inflammatory/irritant changes observed in the upper respiratory tract, a known non genotoxic carcinogenicity mode of action. Therefore, additional uncertainty factors have been included in the calculation of the reference values for the extrapolation of short-term to long-term toxicity.

Reproductive and development toxicity was evaluated in a two-generation reproductive toxicity study conducted in rat, two developmental toxicity studies conducted in rat and one developmental toxicity study conducted in rabbit; all studies were conducted by inhalation. Dimethyl disulfide was not affecting reproductive toxicity parameters and parental toxicity was based on a decrease in body weight and/or food consumption (NOAECs of 5 ppm and 80 ppm for parental and reproductive and offspring, respectively). Dimethyl disulfide is not teratogenic and a developmental NOAEC and maternal NOAEC were set at 20 ppm and 5 ppm, respectively, in the rat studies. The NOAEC values are higher in the rabbit study.

Dimethyl disulfide was neurotoxic in the acute inhalation neurotoxicity study, based on the results of the functional observation battery and locomotor activity evaluations. In a 90-day inhalation neurotoxicity study in rat, the NOAEC for systemic toxicity (decrease in body weight and food consumption) and neurotoxicity (reduced total session motor activity) of dimethyl disulfide was 20 ppm. The NOAEC for local contact (nasal) irritation of dimethyl disulfide was 5 ppm for both males and

[5] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

females. A developmental neurotoxicity (DNT) dose-range finding study (without neurotoxicity investigations in offspring) was also conducted with dimethyl disulfide by inhalation with a LOAEL (systemic and local effects) set at 20 ppm for both maternal (decrease in body weight and food consumption) and developmental toxicity (decrease in body weight gain). A proper DNT study was not conducted with dimethyl disulfide; therefore, the potential higher susceptibility of the pups was not properly investigated. An additional uncertainty factor was therefore applied for the derivation of the reference values considering the lack of data on DNT.

In a 90-day immunotoxicity study in rat, a LOAEC of 10 ppm was derived based on a decreased lymphocyte count, inflammatory lesions in mandibular and popliteal lymph node and splenic lymphoid atrophy. This study was not conducted according to the available guideline and an additional concern on immunotoxicity was raised by the positive skin sensitisation study. Therefore, in the absence of a NOAEC, an immunotoxic potential could not be excluded for dimethyl disulfide (data gap).

The assessment of the endocrine-disrupting potential of dimethyl disulfide was performed based on the new scientific criteria for the determination of endocrine-disrupting properties, as laid down in Commission Regulation (EU) 2018/605[6] and implemented in the EFSA/ECHA guidance (2018) for the identification of endocrine disruptors. Based on the available incomplete data set for dimethyl disulfide, no adverse effects for the thyroid modality (T-modality) and oestrogen, androgen and steroidogenesis modalities (EAS-modalities) were observed. However, in line with the EFSA/ECHA guidance (2018) guidance, the experts agreed that considering the dose-limiting irritant properties of the substance, additional studies are not needed. Therefore, according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that dimethyl disulfide is not an endocrine disruptor in humans.

Dimethyl disulfide is a ubiquitous substance in the environment where it is present in the atmosphere, it is also present in food items and used as a flavouring agent. During the Pesticide Peer Review Expert's Meeting 1 in April 2019, the experts agreed that setting reference values for consumers, related to the agricultural use of dimethyl disulfide, was not considered relevant as no residues of dimethyl disulfide above the quantifiable limit were found in food commodities. However, in line with the assessment reported in Section 3 and considering the amount of dimethyl disulfide in groundwater calculated after the environmental fate expert meeting (see Section 4), EFSA considered that this assumption is not justifiable. It is worth noting that based on the available data, an acceptable daily intake (ADI) and an acute reference dose (ARfD) cannot be derived, due to the lack of oral toxicity studies, the high volatility of the substance and a local dose-limiting toxicity (inflammatory change of nasal mucosa) specific to the route of exposure by inhalation. Therefore, as the toxicological reference values (ADI, ARfD) cannot be defined (data gap), the risk assessment by oral exposure is an issue that could not be finalised (see Section 3).

The acceptable operator exposure concentration (**AOEC**) was derived from the NOAEC of 5 ppm (multigeneration and developmental rat inhalation toxicity studies) corrected by an uncertainty factor of 2,000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation and an additional 20 due to the uncertainties related to the incomplete data set i.e. the lack of a second species in short-term toxicity studies, of a DNT study and of a long-term/carcinogenicity study). Therefore, an AOEC of 0.0025 ppm, equivalent to 0.0096 mg/m^3 (9.6 μg/m^3) was derived. The acute acceptable operator exposure concentration (**AAOEC**) was derived from the local NOAEC of 5 ppm in the 90-day neurotoxicity study conducted by inhalation in rat. This NOAEC was corrected by an uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation and an additional combined uncertainty factor (UF) of 10, considering the lack of a second species in short-term toxicity studies and the lack of a DNT study). Therefore, an AAOEC of 0.005 ppm, equivalent to 0.019 mg/m^3 (19 μg/m^3) was derived.

MSA, HCHO and SO_2 are major air metabolites of dimethyl disulfide. Given the significance of the air environmental compartment for fumigant dissipation, and their local hazardous (irritant) properties, operator, bystander/resident and worker risk assessments were conducted.

MSA is a major water, air and soil metabolite of dimethyl disulfide and is also a component of the proposed metabolic pathway of dimethyl disulfide after ingestion. MSA showed exceedance of 0.1 μg/L in PEC_{gw} calculations in individual FOCUS groundwater scenarios (see Section 4). Although several toxicity studies have been conducted with MSA by inhalation, oral and dermal routes, the genotoxicity studies were only considered acceptable with limitations. Considering the limitations of the genotoxicity

[6] 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.

studies, the experts considered that the data set for genotoxicity is not complete and no conclusion on the genotoxicity potential of MSA can be drawn. Therefore, no reference values can be derived (data gap and issue not finalised), as agreed during the experts' meeting. Furthermore, EFSA notes that based on the available data, an ADI and ARfD cannot be derived also due to the lack of oral toxicity studies, the high volatility of the substance and a local dose-limiting toxicity (inflammatory change of nasal mucosa) specific to the inhalation route of exposure (see issue not finalised in Section 3).

HCHO is a major air metabolite of dimethyl disulfide but is not a metabolite in animals according to the available data. HCHO is classified as follows: Acute Tox. 3 – H331, Acute Tox. 3 – H311, Acute Tox. 3 – H301, Skin Corr. 1B – H314, Skin Sens. 1 – H317, Muta 2 – H341, Carc. 1B – H350[5]. A common toxicological effect of HCHO, also shared by dimethyl disulfide, is the local irritant effect of the nasal mucosa (all species) leading to degenerative and neoplastic findings (rats and monkeys). An AOEC of 120 $\mu g/m^3$ for HCHO for all populations (operators, bystander/residents and workers) is proposed based on combined human and animal data.

SO_2 is irritant for the upper respiratory tract and the proposed reference value for SO_2 is 0.2 ppm or 0.52 mg/m^3, based on human studies in the healthy and asthmatic population (sensitive population). The data set for the assessment of genotoxicity is incomplete. However, a Scientific Opinion of EFSA (EFSA ANS Panel, 2016) exists. Based on the available genotoxicity data, EFSA considered that the use of SO_2 as a food additive did not raise a concern with respect to genotoxicity. The process of assessing SO_2 as a biocide and for classification and labelling purposes is ongoing; therefore, the current conclusion could be revised depending on the outcomes.

The experts agreed to derive the reference values and to revise the exposure calculations for the acute exposure for operators, workers and bystanders; 8-h exposure for workers and operators (with the sum of loading and application tasks); 24-h exposure for residents. The experts also agreed that the data provided mostly considered southern Europe conditions only, and a direct extrapolation of the worker exposure during film removal stage estimations to central and northern countries is not feasible based on the impact of the temperature on production of air metabolites (data gap). EFSA notes that the same applies also for the exposure of the additional populations (operators, bystanders and residents) since all studies were performed in southern Europe.

For the product '**Paladin EC'**, the exposure estimate for operators exceeds the reference value for dimethyl disulfide in greenhouse applications, also using personal protective equipment (respiratory protection equipment (RPE) with an assigned protection factor (APF) of 40). No data are available for operator loading for dimethyl disulfide in greenhouse/tunnel conditions (data gap) though data are available for the loading task performed outside. Data for HCHO exposure estimates are lacking for worker (crop transplant) and operator (loading and fumigation in tunnel and loading and crop transplant in greenhouse (data gaps and issue not finalised). For protected crop uses of 'Paladin EC', the risk assessment cannot be finalised based on non-realistic exposure calculation for MSA and SO_2 and a concern remains for both greenhouse and tunnel (walk-in tunnel conditions data were provided and considered as a possible use under the term 'glasshouse application') conditions (data gap and issue not finalised). Similarly, for workers and residents, when combining the different exposures of dimethyl disulfide and HCHO and use conditions, there is still an exceedance of the reference value. For bystanders, the risk is acceptable for dimethyl disulfide with mitigation measures.

For the product '**Paladin'**, the exposure estimate for operator, workers and residents to dimethyl disulfide exceeds the reference values. For bystanders, the risk is only acceptable for dimethyl disulfide considering an exclusion period of 29 days after application and a minimum distance of 5 m from the treated area. Bystander exposure, following application of drift reduction technology and of a 2–3 m buffer stripe was, however, not considered in the assessment. For HCHO, the assessment could not be finalised due to lack of data or on no acceptable theoretical calculation for operators, workers and bystanders/residents (data gap and issue not finalised). Furthermore, no measurements have been performed for MSA and SO_2 and the exposure assessment cannot be finalised (data gap and issue not finalised).

The overall conclusion is that it is not possible to identify a single acceptable exposure scenario or safe condition of use for all categories of exposed populations (operators, workers and residents) for both 'Paladin' and 'Paladin EC'. This represents a critical area of concern (see further details in the evaluation table, experts' consultation points 2.14 in EFSA, 2019 and Appendix A).

3. Residues

The assessment in the residue section is based on the following guidance documents: OECD (2009, 2011b), European Commission (2011) and JMPR (2004, 2007).

Metabolism studies to address the nature of residues in root and fruit crops and compliant with the representative uses upon soil application of dimethyl disulfide were not submitted. Based on the studies investigating the fate of dimethyl disulfide in soil, the formation of MSA and methanethiol (MT) has been observed (see Section 4). Although no specific plant metabolism studies were submitted, it can be assumed that, considering the chemical structure of dimethyl disulfide and the fate and behaviour of dimethyl disulfide in soil, no additional metabolites besides the metabolites found in soil are expected to be relevant for food crops. Therefore, in addition to MSA, also the soil metabolite MT needs to be considered for its potential plant uptake. Thus, pending on the final soil assessment (see data gaps in Section 4), additional field trials analysing MT and covering the representative crops might also be needed.

Currently, no residue definition could be proposed for monitoring and risk assessment in plants. To establish the residue definition, the outcome of the identified outstanding studies and data in Sections 2 and 4 will need to be considered (see Section 7 for the data gaps).

As regards the field trials analysing for the magnitude of dimethyl disulfide residues, in addition to the SEU residue trials (four in strawberries, four in tomatoes and four in carrots), additional overdosed US residue trials (896 kg/ha vs. 400 kg/ha for representative GAPs) in strawberries, tomatoes, carrots and radish were also submitted. In all the trials except radish, the residue levels of dimethyl disulfide were reported as < 0.01 mg/kg. It should be noted however, that the experimental design of the trials was not fully compliant with the representative GAPs as the tight film covering the soil after application of dimethyl disulfide was kept only for 7 days instead of 21 days. Moreover, some deficiencies have been identified in the analytical part of the studies. As reported by the study authors, the extracted samples were kept before the analysis up to three days at temperatures between 0°C and 9°C and therefore further degradation/dissipation of dimethyl disulfide residues cannot be excluded. Thus, sufficient field residue trials analysing dimethyl disulfide, compliant with the representative GAPs in carrots (SEU and NEU) and tomatoes, covered by storage stability data and validated analytical method need to be provided (data gap). The metabolite MSA was analysed only in the SEU trials and the residue levels were found all below the LOQ. However, the LOQ of the analytical method was very high in tomatoes (0.4 mg/kg) and in carrots (0.5 mg/kg). Since based on the available data, no conclusion on the genotoxic potential of MSA can be drawn and toxicological reference values cannot be set (see data gap in Section 2), currently a consumer dietary risk assessment to this compound cannot be conducted. Therefore, pending on the outcome of the requested data to address the genotoxicity and general toxicity of MSA (see Section 2), sufficient GAP-compliant residue trials in tomatoes and carrots and analysing for this compound with a method validated at an appropriate lower LOQ may need to be requested.

Storage stability data at <– 18°C were submitted in carrots, tomatoes and strawberries demonstrating the stability of residues for dimethyl disulfide and metabolite MSA for 8 and 3 months, respectively. Since samples of the residue trials on carrots, tomatoes and strawberries were stored frozen for 6 months before analysis, the integrity of the residues of MSA during storage cannot be demonstrated. Therefore, additional storage stability data on MSA, covering the maximum storage time interval of the samples of the residue trials on carrots and tomatoes are required (data gap).

Currently, processing studies are not available and a livestock exposure assessment was not conducted but might need to be reconsidered pending on the overall data requested through the different sections (see Sections 2 and 4).

In addition, the consumer risk assessment through dietary intake and drinking water is not finalised considering the lack of reference values (see Section 2) and the lack of appropriate information to address the effect of water treatment processes on the nature of residues of the active substance and its possible metabolites, potentially present in surface water and groundwater, when surface water or groundwater is abstracted for drinking water. Besides, the possibility of groundwater contamination at levels above the parametric drinking water limit of 0.1 μg/L cannot be excluded for dimethyl disulfide (see Section 4). The consumer risk assessment through drinking water for MSA could not be finalised either, in the absence of toxicological data to address the genotoxicity and general toxicity of this compound (see Section 2).

Overall, the consumer risk assessment through dietary intake and drinking water could not be finalised in view of the identified data gaps and considering that no toxicological reference values are derived for dimethyl disulfide and that the toxicological relevance of the metabolite MSA is currently open (see Sections 2 and 4).

The argumentation that dimethyl disulfide should be included in Annex IV of Regulation 396/2005 due to its natural occurrence and the fact that this substance is also used as a flavouring agent is therefore not fully supported.

4. Environmental fate and behaviour

Dimethyl disulfide was discussed at the Pesticides Peer Review Experts' Meeting 2 in April 2019.

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, dimethyl disulfide exhibited low to moderated persistence (according to updated estimations provided by the RMS after the experts' consultation). Degradation of dimethyl disulfide results in the formation of the major metabolite MSA (max. 33.2% applied radioactivity (AR)). However, the reliability of the dissipation and degradation kinetic parameters obtained for dimethyl disulfide in laboratory studies is compromised by the high volatility observed in the laboratory system and the incomplete characterisation of the volatilised radioactivity. The formation of other major volatile metabolites (e.g. HCHO and SO_2) cannot be excluded and a data gap for further investigation of the identity of these volatiles has been identified. The metabolite MSA exhibited apparent low persistence in soil under field conditions. It is noted that reliable $DegT_{50}$ values cannot be obtained for dimethyl disulfide from the available field dissipation data sets. Consequently, the reliability of the kinetic dissipation parameters of the subsequent metabolites such as MSA is also compromised. Therefore a data gap has been identified during the peer review for a laboratory aerobic degradation study in soil with metabolite MSA. Mineralisation to carbon dioxide accounted for 8.3–30.8% AR after 120 days. The formation of unextractable residues accounted for 0.13–8.21% AR after 120 days. In anaerobic soil incubations, dimethyl disulfide is degraded to metabolite MT (max. 16% AR after 14 days). The experts agreed that the occurrence of anaerobic, or partial anaerobic conditions, during the period the soil is covered cannot be excluded according to the information available in the public scientific literature. Therefore, a data gap was identified for the exposure and risk assessment of the soil anaerobic metabolite MT formed under anaerobic conditions. Consequently, also information on the degradation of this metabolite in soil is needed to finalise the exposure (all environmental compartments including groundwater) and risk assessment.

From the batch adsorption/desorption study results it can be considered that dimethyl disulfide is very highly mobile in soil. The peer review identified a data gap for an adsorption study with the metabolite MSA. Also, information on the adsorption/desorption of metabolite MT was not available. This information is needed to address the data gap identified during the peer review for the exposure and risk assessment of this anaerobic metabolite.

Dimethyl disulfide was stable to hydrolysis in the range of environmentally relevant pHs (5–9) at temperatures up to 50°C. Dimethyl disulfide is not readily biodegradable. Photolysis may partially contribute to the degradation of dimethyl disulfide in aqueous media. Metabolites formed during aqueous photolysis were not adequately characterised. Therefore, a data gap was identified for the characterisation of the major aqueous photolysis products. No acceptable incubations in dark aerobic natural sediment water systems have been provided for dimethyl disulfide. During the peer review, a data gap for water sediment studies performed with adequate design to investigate degradation of dimethyl disulfide in the aquatic environment was identified, leading to assessments not finalised.

After the experts' consultation the RMS presented new PEC_{SW}/PEC_{sed} calculations for dimethyl disulfide performed at FOCUS step 3 level considering volatilisation and redeposition and two alternative approaches:

- Using soil $DegT_{50}$ for dimethyl disulfide and letting volatilisation be simulated by the model.
- Using soil $DissT_{50}$ for dimethyl disulfide and setting volatilisation to 0 to prevent double counting of volatilisation.

In addition, there is a high uncertainty on the degree of degradation and type of conditions existing during the period the soil is covered. Consequently, both calculations have been performed assuming that degradation occurs while the soil is covered (based on DT_{50}'s calculated by the RMS for aerobic studies) and that no degradation occurs during the time the soil is covered. This results in a set of four

environmental exposure calculations for each use. PEC_{SW} contribution by volatilisation deposition was added to the run-off/drainage calculations produced according to the above alternatives. Each of these approaches were considered to be subject to a great deal of uncertainty. On the one hand, FOCUS models have not been calibrated for highly volatile substances; on the other hand, laboratory experiments, such as the ones used to determine dissipation and degradation of dimethyl disulfide in soil, may overestimate volatilisation due to the relative low amount of soil used. In addition, it is not possible to confirm that aerobic conditions are maintained when the soil is covered. Nevertheless, the experts agreed that these set of values could represent a range of realistic worst-case PEC_{SW} that can occur after the use of dimethyl disulfide. For the metabolite MSA, the RMS provided FOCUS step 3 PEC_{SW}/PEC_{sed} calculations based on the maximum occurrence observed in soil studies. FOCUS step 4 PEC_{sw} considering run-off mitigation measures (20 m vegetated buffer zones, only applicable to R scenarios) were calculated. Deposition of other potential volatile metabolites (such as HCHO and SO_2) to surface water was not addressed by the available exposure assessment (data gap and issue not finalised).

After the experts' consultation, the RMS also presented new PEC_{GW} calculations using the same range of approaches considered for the modelling of surface water exposure. The potential for groundwater exposure from the representative field use in carrots was calculated using FOCUS (FOCUS, 2009) scenarios and the models PEARL 4.4.4 and PELMO 5.5.3. Taking into account all the uncertainties, the possibility of groundwater exposure by dimethyl disulfide and MSA at levels above the parametric drinking water limit of 0.1 μg/L cannot be excluded. Even when the most favourable assumptions are considered, the limit of 0.1 μg/L is exceeded in the majority of the six relevant scenarios for the spring application. The greenhouse use in tomatoes was considered to be represented and covered by the simulations performed for the use in carrots when no degradation under the barrier film (tarpaulin or tarp) is assumed (400 kg a.s./ha application). A critical area of concern has been identified with respect to potential ground water contamination by dimethyl disulfide above the parametric value of 0.1 μg/L. PEC_{GW} was also estimated for the soil metabolite MSA. Due to the lack of reliable experimentally measured data (see data gaps identified), the calculations were performed using worst case assumptions. The limit of 0.1 μg/L is also exceeded by this metabolite in all pertinent scenarios. The groundwater relevance assessment of this metabolite remains open due to the data gap identified in Section 2, leading to an assessment not finalised.

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

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

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009).

Dimethyl disulfide was discussed at the Pesticides Peer Review Experts' Meeting 3 in April 2019.

Acute oral data for dimethyl disulfide were available for both **birds** and **wild mammals**.

For uses in permanent greenhouse, no oral exposure to wild terrestrial vertebrates is anticipated, and hence the risk is considered as low.

For all the other uses, including those on non-permanent protected crops, exposure cannot be excluded, and a risk assessment is needed. A specific scenario for the applications described in the GAP (shank injection, drip irrigation) is not available in EFSA (2009). In order to assess the risk, the 'bare soil scenario' for spray applications has been used. Based on such scenario, at the tier 1, a high acute risk had been identified for all the relevant generic focal species of both birds and wild mammals.

A number of refinements were made available, considering different scenarios. All of these refinements were discussed in the experts' meeting,[7] where the experts agreed that some of the assumptions used in these assessments were too weak and unsupported by sound data (e.g. assuming that invertebrates could be eaten only after tarp removal; assuming that only contaminated

[7] See expert consultation point 5.2 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).

soil would be ingested, etc.). The only scenario considered acceptable by the experts was the one where the residues in the food items were set as equal to the PEC_{soil}. This was considered a worst-case, in view of the scarce lipophilicity of dimethyl disulfide. Nevertheless, even when considering this refinement, a high acute risk could not be excluded. In addition, the experts considered that the risk to vermivorous species should be explicitly addressed (data gap). For birds, a risk assessment specific to oystercatcher was carried out, as these species were spotted in one study to actively pierce the tarp and forage. Also, in this case, the residues in food items were set equal to the PEC_{soil}. The assessment resulted in a TER < 10, and hence high acute risk could not be excluded. Therefore, a critical area of concern has been identified for birds and mammals.

Appropriate chronic oral endpoints were not available for either birds or wild mammals (data gap). The experts at the meeting[8] considered that a chronic exposure cannot be ruled out, hence the assessment could not be finalised.

A low risk for all uses of dimethyl disulfide was concluded for both birds and wild mammals from exposure via secondary poisoning (log P_{ow} = 1.91) and via consumption of contaminated water.

Due to the volatile nature of dimethyl disulfide and its air metabolites (HCHO, MSA, SO_2) a risk assessment for exposure via inhalation was also considered relevant for all applications (also those in permanent greenhouses). Acute inhalation studies were available for birds and mammals, and for the latter also a two-generation study with the same route of exposure was available. The experts at the meeting noted that there was a major uncertainty with regard to the inhalation exposure as the amount of air breath by the animals was not considered, neither in the endpoint from the inhalation studies nor in the field exposure estimate. These uncertainties were considered to be too high to conclude a low risk.[9] In addition, explicit consideration of the air metabolites of dimethyl disulfide was missing (data gap). Overall, the acute and long-term inhalation risk assessment was not considered finalised.

Suitable data were available for assessing the acute toxicity of the active substance dimethyl disulfide to **fish** and **aquatic invertebrates**. On the contrary, none of the available chronic studies for the same groups of organisms was considered reliable (data gap). Three studies were available to characterise the toxicity of dimethyl disulfide to **algae**, nevertheless none of them fulfilled the validity criteria set out in OECD 201 (OECD, 2011a). The RMS suggested that these studies could still be used for the risk assessment, but such approach is not accepted and therefore a data gap is identified. One valid study was available for **macrophytes**.

As already mentioned in Section 4, there were significant uncertainties in the prediction of the exposure level in surface waters for the use of dimethyl disulfide in the field and in non-permanent protected crops. The experts in the fate area accepted a range of values obtained with four different options, combining different input parameters of the FOCUS models (see Section 4). The risk assessment using FOCUS step 3 PEC_{sw} was carried out with each of the options, in order to illustrate the uncertainty around the final risk assessment.

For the uses in open fields and non-permanent protected crops, the acute risk assessment for fish using FOCUS step 3 PEC_{sw} resulted in a high risk in the majority of the scenarios (5 out of 6), with minor differences between the four approaches for calculating the exposure. The outcome of the acute risk assessment was similar for aquatic invertebrates, with high risk identified in 4–5 out of 6 scenarios, depending on the approach. FOCUS step 4 PEC_{sw} considering mitigation measures (20 m vegetated buffer zones) were available for the four R scenarios. It is worth noting that for one of the D scenarios (D6) the risk was not addressed at the step 3 for neither fish nor invertebrates. The available step 4 PEC_{sw} only considered 2 out of 4 approaches used at step 3. High acute risk was still identified for fish (in 3–4 out of 4 scenarios) and invertebrates (2–4 out of 4 scenarios), leading to the identification of a critical area of concern.

For use in permanent greenhouses, a low acute risk was identified for both fish and aquatic invertebrates using PEC_{sw} calculated at FOCUS step 3.

A chronic risk assessment could not be finalised for fish, invertebrates and algae, due to the lack of reliable hazard data.

A low risk to aquatic macrophytes was concluded for all uses of dimethyl disulfide using PECsw calculated at step 1.

Valid acute toxicity data on fish and aquatic invertebrates were available for the soil metabolite MSA, while no valid chronic data were available for any group of organisms (data gap). For the uses in open field and non-permanent protected crops, a low acute risk was identified for aquatic invertebrates on

[8] See expert consultation point 5.1 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).
[9] See expert consultation point 5.3 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).

the basis of PEC_{sw} calculated at step 2. A low acute risk was also identified for fish in 5 out of 6 scenarios using PEC_{sw} calculated with FOCUS step 3. PEC_{sw} for the uses in permanent greenhouses were not provided, but this assessment is considered to be covered by the use in open field.

No information on both toxicity and exposure was provided for the anaerobic soil metabolite MT (data gap). No suitable data are available to address the risk to aquatic organisms due to redeposition of air metabolites SO_2 and HCHO (data gap).

Data on the toxicity of dimethyl disulfide to **honeybees** were available for acute contact exposure. No oral data were available (data gap). Since dimethyl disulfide is used as a fumigant in bare soil, contact and oral exposure in the treated field is considered negligible. However, redeposition of dimethyl disulfide cannot be excluded in the off-field[10] (see Section 4); therefore, the need for an assessment of areal deposition was identified for all uses (including those in permanent greenhouse), as also acknowledged by the ecotoxicology experts at the peer review meeting.[11] In the DAR, an approach for addressing the contact exposure resulting from off-field redeposition was presented. The exposure estimate is based on a field flux study with dimethyl disulfide. However, this study presented some important uncertainties highlighted by the fate experts[10]. During the ecotoxicology peer review meeting, the experts agreed that the available information on exposure was not sufficient to conclude on the risk to bees[11] (data gap). Nevertheless, if the off-field redeposition value used for the illustrative risk assessment would be confirmed to be reliable (or representing a worst-case), a low contact risk could be concluded.

In addition, exposure via inhalation was deemed relevant for all uses. A 4-h acute inhalation test was available. The RMS provided a comparison between the measured air concentration of dimethyl disulfide in the field flux study with the predicted LC_{50} range from the acute inhalation toxicity study. Such comparison indicates that the predicted exposure is around a factor of 10 lower than the estimated LC_{50}. Nevertheless, in lack of a specific risk assessment scheme and considering the significant uncertainties regarding the exposure, no firm conclusion can be drawn (assessment not finalised).

No data on the standard species of foliar dwelling **non-target arthropods** were available (data gap). The waiver presented by the applicant for considering soil macroorganisms as surrogates to address the risk for leaf-dwelling organisms was not accepted at the ecotoxicology peer review meeting[11]. As for bees, exposure in field is not anticipated, but exposure via redeposition to the off-crop environment cannot be excluded for all uses (including those in permanent greenhouse). In view of the lack of specific toxicity data and the uncertainty related to the exposure, the risk assessment for foliar dwelling non-target arthropods cannot be finalised.

Laboratory studies with dimethyl disulfide were available for **earthworms** (acute) and **other soil macroorganisms**: *Hypoaspis aculeifer* (chronic), *Folsomia candida* (chronic + aged residues) and *Poecilus cupreus* (acute).

Concentrations had been measured uniquely at the beginning of the acute earthworm study and they were significantly lower than the nominal ones. The experts at the peer review meeting considered that: (i) clear effects were seen in all laboratory studies; and (ii) the fast volatilisation of the substance together with the standard application in laboratory test (i.e. mixing) caused the endpoints based on nominal or initial concentrations not to be sufficiently reliable for the risk assessment.[12] Hence, no valid laboratory data are available for any soil macroorganism (data gap). However, for earthworms, two field studies were available. These were discussed during the peer review meeting.[13] The experts at the meeting agreed that recovery at least within 1 year was not demonstrated in the studies, as some clear effects were still observed after one year.

For uses in permanent greenhouse, the exposure is predicted to be negligible, and a low risk can be concluded for all soil macroorganisms.

For the other uses (open field and non-permanent protected crops), based on the results of the field studies, a low risk for earthworms cannot be concluded, therefore, a critical area of concern was identified. For the other soil macroorganisms, in lack of reliable data, the risk assessment cannot be finalised. No data are available for the soil metabolite MSA and for the anaerobic soil metabolite MT (data gap).

Two studies with dimethyl disulfide and **soil microorganisms** were available, where concentrations were measured at the beginning and at the end of the exposure phase. Slightly more than 25% (i.e.

[10] See expert consultation point 4.6 from the report of the Pesticides Peer Review Experts' Meeting 02 (EFSA, 2019).
[11] See expert consultation point 5.4 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).
[12] See expert consultation point 5.5 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).
[13] See expert consultation point 5.6 from the report of the Pesticides Peer Review Experts' Meeting 03 (EFSA, 2019).

26%) effect (stimulation) on soil nitrogen transformation rate was still observed at the end of the relevant study, 28 days after the application. However, considering the decreasing trend of the observed effect and the fact that the initial tested concentration was more than a factor of 40 greater than the maximum predicted PEC_{soil}, a low risk to soil microorganisms can be concluded for all uses of dimethyl disulfide.

Data were available to assess the toxicity of dimethyl disulfide to **non-target terrestrial plants**. Exposure is predicted to be driven by redeposition to the off-field environment. The exposure estimate used by the RMS in the risk assessment is based on a field flux study with dimethyl disulfide. As already pointed out before, this study presented some uncertainties highlighted by the fate experts.[10] During the ecotoxicology peer review meeting, the experts agreed that the available information on exposure was not sufficient to conclude on the risk to non-target terrestrial plants (data gap). Nevertheless, if the off-field redeposition value used for the illustrative risk assessment would be confirmed to be reliable (or representing a worst-case), a low risk to plants could be concluded for all uses of dimethyl disulfide with a large margin of safety (a factor > 450).

One study was available for assessing the effects of dimethyl disulfide to **activated sludge**. However, the test vessel was stirred for 22 h before the addition of the inoculum. Considering the volatility of dimethyl disulfide, it is likely that the inoculum was exposed to very low (and non-quantifiable) concentrations of dimethyl disulfide. Hence, the effects of biological methods for sewage treatment cannot be reliably assessed (data gap).

With regard to the assessment of **endocrine disruption (ED) potential** according to ECHA/EFSA Guidance (2018), as reported in Section 2, dimethyl disulfide is not an endocrine disruptor in humans and this conclusion also applies to mammals as non-target organisms.

For non-target organisms other than mammals, no long-term studies were available and thus the available data set was not complete for assessing potential ED-mediated adversity. Furthermore, only ToxCast data were available regarding endocrine activity for the EATS modalities. Thus, the available evidence was not considered sufficient to draw a conclusion on the endocrine-disrupting properties for non-target organisms (data gap and issue not finalised).

Following the assessment strategy proposed in the ECHA/EFSA Guidance (2018), level 3 and 4 tests would be required to complete the current data package, i.e. a study in line with OECD TG 231 Amphibian Metamorphosis Assay (AMA) and a study in line with the OECD TG 234 Fish Sexual Development Test (FSDT). This latter test would be preferable to a test in line with OECD 229 as, in the specific case of dimethyl disulfide, it can also be used for risk assessment purpose.

The requested tests are relevant to investigate potential EATS-mediated endocrine activity and, if negative, to exclude that dimethyl disulfide has endocrine properties, according to the scientific criteria for the determination of endocrine-disrupting 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. However, in case of positive result/s based on these tests for at least one modality, additional testing (i.e. a test in line with OECD 241 and/or a test in line with OECD 240) might be needed in order to further investigate the adversity.

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Dimethyl disulfide	Low to moderate (DT_{50} = 4.6 – 27.6 days)	High risk to soil organisms (earthworms)
Methanesulfonic acid (MSA)	Degradation half-lives not calculated	Data gap
Methanethiol (anaerobic metabolite)	Degradation half-lives not calculated	Data gap

DT_{50}: period required for 50% dissipation (define method of estimation).

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[a]	Pesticidal activity	Toxicological relevance
Dimethyl disulfide	Very high (K_{Foc} = 9–41 mL/g)	FOCUS: Yes. All scenarios (6 of 6) > 0.1 µg/L. 400 kg/ha to carrots 84.5–1,039.7 µg/L; 75 kg/ha[b] 9.11–155.5 µg/L	Yes	Yes
Methanesulfonic acid (MSA)	No data available (default values used for exposure estimation)	FOCUS: Yes. All scenarios (6 of 6) > 0.1 µg/L. 17.58–1,371.64 µg/L	No data	Open, data needed to set reference values and clarify genotoxicity potential
Methanethiol (anaerobic metabolite)	No data available	Not calculated	No data	No data available

K_{Foc}: Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use.
(a): At least one FOCUS scenario or a relevant lysimeter.
(b): corrected application rate after 21 days of soil tarping.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Dimethyl disulfide	High risk to aquatic organisms living in the surface water
Methanesulfonic acid (MSA)	Data gap
Methanethiol (anaerobic metabolite)	Data gap
Formaldehyde	Data gap
Sulfur dioxide	Data gap

Table 4: Air

Compound (name and/or code)	Toxicology
Dimethyl disulfide	> 3.26 mg/L air/4 h and 2–10 mg/L DMDS as vapour (Acute Tox. 3, H331), NOAEC 34.7 mg/m^3 (STOT SE 1 H370) Two-generation rat study: NOAEC = 5 ppm (19 mg/m^3) based on decreased bodyweight gain and/or food consumption Developmental rat study: NOAEC = 5 ppm (19.25 mg/m^3) based on decreased bodyweight gain 90-day rat neurotoxicity study: Local NOAEC = 5 ppm (19.25 mg/m^3) based on nasal irritation
Methanesulfonic acid (MSA)	28-day inhalation rat study: NOAEC Systemic = 0.073 mg/L; LOAEC Local = 0.026 mg/L
Methanethiol (anaerobic metabolite)	No data available
Formaldehyde (tentatively identified in operators and workers field studies)	Acute Tox. 3 – H331 AOEC = 120 μg/m^3 based on human sensory irritation study and animal studies
Sulfur dioxide (tentatively identified in operators and workers field studies)	AOEC = 520 μg/m^3 based on human health effects

NOAEC: no observed adverse effect concentration; LOAEC: lowest observable adverse effect concentration; AOEC: acceptable operator exposure concentration.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of the Regulation concerning information on potentially harmful effects).

- A search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, including also MSA, dealing with side effects on health, the environment and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA (2011) guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (relevant for all representative uses evaluated; relevant for Sections 2, 3, 4 and 5).
- Confirmatory method for the determination of dimethyl disulfide in surface water and ground water (relevant for all representative uses; see Section 1).
- Monitoring method for the determination of MSA in drinking water (relevant for all representative uses; see Section 1).
- Monitoring methods for the determination of residues of MSA, SO_2 and HCHO in the air (relevant for all representative uses; see Section 1).
- A monitoring method is not available for $DMSO_2$, which was identified as a suitable marker for monitoring in body fluids (data gap would be relevant under the new data requirements in accordance with Commission Regulation (EU) No 283/2013; relevant for all representative uses; see Sections 1 and 2).
- Additional data are needed to address immunotoxicity (relevant for all representative uses; see Section 2).
- Based on the available data, an ADI and an ARfD cannot be derived for dimethyl disulfide due to the lack of oral toxicity studies, the high volatility of the substance and a local dose-limiting toxicity (inflammatory change of nasal mucosa) specific to the route of exposure by inhalation. Therefore, toxicological data are needed for setting reference values (relevant for all representative uses; see Sections 2 and 3).
- Additional data are needed for the exclusion of a genotoxic potential of the major aqueous, soil and air metabolite MSA. In addition, toxicological data are needed for setting reference values (ADI, ARfD) (relevant for all representative uses; see Sections 2 and 3).
- Exposure data of operators, workers, bystanders and residents in the central and northern countries (relevant for all representative uses; see Section 2).
- Exposure data for loading task for dimethyl disulfide (relevant for 'Paladin EC'; see Section 2).
- Data for operator (loading and fumigation in tunnel and loading and crop transplant in greenhouse) and worker (crop transplant) for HCHO exposure estimates are lacking (relevant for 'Paladin EC'; see Section 2).
- Exposure data for MSA and SO_2 for operators, workers and bystanders/residents (relevant for 'Paladin' and 'Paladin EC'). In addition, exposure data for HCHO are needed for 'Paladin' for operators, workers and bystanders/residents (see Section 2).
- Sufficient GAP-compliant residue trials in carrots (SEU and NEU) and tomatoes analysing for dimethyl disulfide covered by storage stability and a validated analytical method were not available (relevant for all representative uses; see Section 3).
- Storage stability studies for MSA to cover the whole storage period of the residue samples of the residue trials on carrots and tomatoes (relevant for all representative uses; see Section 3).
- Investigation of the identity of volatiles formed after the degradation of dimethyl disulfide in soil (relevant for all representative uses; see Section 4).
- Laboratory aerobic degradation study in soil for the metabolite MSA (relevant for all representative uses; see Section 4).
- Data (degradation and adsorption) to assess the environmental exposure and the risk of the soil anaerobic metabolite MT formed under anaerobic conditions were not available (relevant for all representative uses; see Sections 4 and 5).
- A batch soil adsorption study with metabolite MSA was not available (relevant for all representative uses; see Section 4).

- Characterisation of the major aqueous photolysis products was not available (relevant for all representative uses; see Section 4).
- Water sediment studies performed with an adequate design to investigate the degradation of dimethyl disulfide in the aquatic environment were not available (relevant for all representative uses; see Section 4).
- Environmental exposure assessments taking into account redeposition of volatile soil metabolites other than MSA were not available (relevant for all representative uses; see Section 4).
- Data to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water were not available (relevant for all representative uses; see Section 4).
- The risk to vermivorous species of birds and wild mammals was not adequately explicitly addressed. (relevant for all the representative uses except those in permanent greenhouse, see Section 5).
- Reproductive toxicity data (oral exposure) of birds and wild mammals were missing (relevant for all the representative uses except those in permanent greenhouse, see Section 5).
- Suitable data to address the risk to birds and wild mammals from inhalation of dimethyl disulfide and its air metabolites (relevant for all the representative uses, see Section 5).
- Reliable chronic data for aquatic organisms (fish, invertebrates, and algae) were missing for dimethyl disulfide and MSA (relevant for all the representative uses, see Section 5).
- Data to assess the risk to aquatic organisms for the anaerobic soil metabolite MT were not available (relevant for all the representative uses, see Section 5).
- Suitable data were not available to address the risk to aquatic organisms due to redeposition of air metabolites SO_2 and HCHO (relevant for all the representative uses, see Section 5).
- Acute oral toxicity data for honeybees were missing (relevant for all the representative uses, see Section 5).
- Data on the standard species of foliar dwelling non-target arthropods were not available (relevant for all the representative uses, see Section 5).
- The exposure to the off-field environment due to redeposition of dimethyl disulfide needs to be properly characterised. This is needed for assessing the risk to off-field organisms such as: bees, leaf-dwelling non-target arthropods and non-target terrestrial plants (relevant for all the representative uses, see Section 5).
- Valid laboratory data were not available for any soil macroorganism exposed to dimethyl disulfide and its soil metabolites (relevant for all the representative uses except those in high technology (permanent) greenhouse, see Section 5).
- A valid and reliable study assessing the effects of dimethyl disulfide on biological methods for sewage treatment was not available (relevant for the representative uses in permanent greenhouse, see Section 5).
- A test according to OECD 231 and a test according to OECD 234 would need to be provided for further investigating the ED potential of dimethyl disulfide (assuming that these 2 tests are performed in parallel, the applicant would need to complete the data package to support a conclusion on absence of EATS-mediated adversity/endocrine activity within a period not exceeding 19 months). However, if one of these tests is positive, further test according to OECD 241 and/or OECD 240 might be needed in order to further investigate the adversity and an additional time period of 28 months would be needed. Relevant for all the representative uses, see Section 5).

8. Particular conditions proposed to be taken into account to manage the risk(s) identified

- For bystanders the risk is acceptable for dimethyl disulfide with mitigation measures for both products (see Section 2, Appendix A and the Evaluation table in EFSA, 2019).

9. Concerns

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of the Regulation and as set out in Commission Regulation (EU) No 546/2011[14] 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 the Regulation.

1) Regarding the southern uses, the risk assessment for dimethyl disulfide for operators cannot be finalised for greenhouse uses. The risk assessment cannot be finalised for HCHO for workers and for operators for loading, fumigation in tunnel and loading and crop transplant in greenhouse ('Paladin EC') (see Section 2).
2) Regarding the southern uses, the risk assessment for MSA, SO_2 cannot be finalised for the field and greenhouse uses ('Paladin' and 'Paladin EC'). In addition, the risk assessment for HCHO cannot be finalised for operators, workers and bystanders/residents for the field uses ('Paladin') (see Section 2).
3) In the central and northern countries, the risk assessment for non-dietary exposure (operators, workers, bystanders and residents) could not be finalised due to lack of data (see Section 2).
4) The consumer dietary risk assessment could not be finalised due to the outstanding data and the lack of reference values for dimethyl disulfide. The consumer risk assessment through drinking water could not also be finalised in relation to the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. Besides, the possibility of groundwater contamination at levels above the parametric drinking water limit of 0.1 μg/L cannot be excluded for dimethyl disulfide (see Sections 2, 3 and 4).
5) The consumer risk assessment through dietary intake and drinking water for MSA metabolite could also not be finalised, in view of the identified data gaps and considering that its toxicological relevance is currently open. This means that the groundwater relevance assessment for MSA is also not finalised (see Sections 2, 3 and 4).
6) Environmental exposure and risk assessment with respect to other volatile metabolites (e.g. HCHO and SO_2) and metabolites that may be identified in the pending studies in water (see Sections 4 and 5).
7) Exposure and risk assessment of metabolite MT, expected to be formed under anaerobic conditions that may exist during the period the soil is tarp covered, could not be finalised (see Sections 4 and 5).
8) The long-term dietary risk to birds and wild mammals could not be finalised, due to lack of toxicity data (see Section 5).
9) The risk from inhalation of dimethyl disulfide and its air metabolites to birds and mammals could not be finalised, due to uncertainties in the exposure and in the quantification of the endpoints in the available toxicity studies (see Section 5).
10) A chronic risk assessment for aquatic organisms could not be finalised due to lack of toxicity data (see Section 5).
11) In lack of a specific risk assessment scheme and considering the significant uncertainties regarding the exposure, the risk assessment to bees for exposure via inhalation could not be finalised (see Section 5).
12) In view of the lack of specific toxicity data and the uncertainty related to the off-field exposure, the risk assessment for foliar dwelling non-target arthropods cannot be finalised (see Section 5).

[14] 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.

13) Due to the lack of reliable toxicity data, the risk assessment for soil macroorganisms other than earthworms could not be finalised (see Section 5).
14) The assessment of the endocrine-disrupting properties of dimethyl disulfide for non-target organisms could not be finalised due to the lack of suitable data (see Section 5).

9.2. Critical areas of concern

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

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at a lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of the Regulation.

15) It is not possible to identify a single exposure scenario or condition of use that is indicated as safe for all categories of the exposed population (operators, workers and residents) for both 'Paladin' and 'Paladin EC') (see Section 2).
16) Potential groundwater exposure above 0.1 μg/L by the active substance dimethyl disulfide (see Section 4).
17) A high acute risk was identified for birds and mammals (see Section 5).
18) A high acute risk to fish and aquatic invertebrates was identified (see Section 5).
19) On the basis of the two available field studies, a low risk for earthworms could not be concluded (see Section 5).

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

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

In addition to the issues indicated below, the assessment of the endocrine-disrupting properties of dimethyl disulfide for non-target organisms according to the scientific criteria for the determination of endocrine-disrupting 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.

Table 5: Overview of concerns

Representative use		Carrot (F)	Tomato (G)
Operator risk	Risk identified	X15	X15
	Assessment not finalised	X2 (for HCHO, MSA, SO_2), X3	X1, X2 (for MSA, SO_2, and HCHO), X3
Worker risk	Risk identified	X15	X15
	Assessment not finalised	X2 (for HCHO, MSA, SO_2), X3	X1, X2 (for MSA, SO_2, and HCHO), X3
Resident/bystander risk	Risk identified	X15**	X15**
	Assessment not finalised	X2 (for HCHO, MSA, SO_2), X3	X2 (for MSA, SO_2), X3
Consumer risk	Risk identified		
	Assessment not finalised	X4, X5	X4, X5

Representative use		Carrot (F)	Tomato (G)
Risk to wild non-target terrestrial vertebrates	Risk identified	X17	X17*
	Assessment not finalised	X8, X9	X8*, X9
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X19	X19*
	Assessment not finalised	X7, X11, X12, X13	X7*, X11, X12, X13*
Risk to aquatic organisms	Risk identified	X18 (4–5 out of 6 scenarios)	X18* (4–5 out of 6 scenarios)
	Assessment not finalised	X6, X7, X10	X6, X7, X10
Groundwater exposure to active substance	Legal parametric value breached	X16	X16
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached[(a)]		
	Parametric value of 10 µg/L[(b)] breached		
	Assessment not finalised	X5, X7	X5, X7

The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2. Where there is no superscript number, see Sections 2–6 for further information.
*: Not applicable for permanent greenhouse.
**: Residents only.
(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.
(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

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Abbreviations

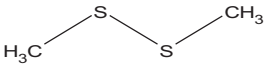
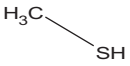
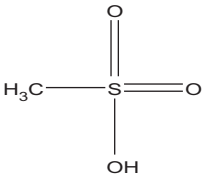
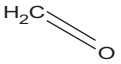
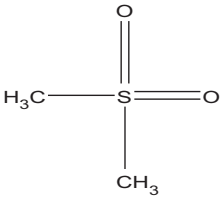
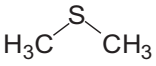
a.s.	active substance
AAOEC	acute acceptable operator exposure concentration
ADI	acceptable daily intake
ADME	absorption, metabolism, distribution and elimination
AL	applied undiluted
AMA	Amphibian Metamorphosis Assay
AOEC	acceptable operator exposure concentration
APF	assigned protection factor
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
DMS	dimethyl sulfide
DNT	developmental neurotoxicity
DT_{50}	period required for 50% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis modalities

EC	emulsifiable concentrate
ECHA	European Chemicals Agency
ED	endocrine disruption
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSDT	Fish Sexual Development Test
GAP	Good Agricultural Practice
GC	gas chromatography
InChiKey	International Chemical Identifier Key
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
LLNA	local lymph node assay
MRL	maximum residue level
MSA	methanesulfonic acid
MT	methanethiol
NEU	northern Europe
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
P_{ow}	partition coefficient between *n*-octanol and water
QSAR	quantitative structure–activity relationship
RMS	rapporteur Member State
RPE	respiratory protective equipment
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
TER	toxicity exposure ratio
UF	uncertainty factor
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2019.5905

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
dimethyl disulfide (DMDS)	dimethyl disulfide CSSC WQOXQRCZOLPYPM-UHFFFAOYSA-N	
methanethiol (methyl mercaptan) (MT)	methanethiol CS LSDPWZHWYPCBBB-UHFFFAOYSA-N	
methanesulfonic acid (MSA)	methanesulfonic acid CS(=O)(=O)O AFVFQIVMOAPDHO-UHFFFAOYSA-N	
formaldehyde (HCHO)	formaldehyde C=O WSFSSNUMVMOOMR-UHFFFAOYSA-N	
dimethyl sulfone ($DMSO_2$)	dimethyl sulfone CS(C)(=O)=O HHVIBTZHLRERCL-UHFFFAOYSA-N	
dimethyl sulfide (DMS)	dimethyl sulfide CSC QMMFVYPAHWMCMS-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).