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CONCLUSION ON PESTICIDES PEER REVIEW

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

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The declarations of interest of all scientific experts active in EFSA's work are available at https://open.efsa.europa.eu/experts

Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Czech Republic and co-rapporteur Member State Hungary for the pesticide active substance daminozide are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The conclusions were reached on the basis of the evaluation of the representative uses of daminozide as a plant growth regulator in ornamentals (field and greenhouse). The reliable end points, appropriate for use in regulatory risk assessment, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

KEYWORDS

daminozide, peer review, pesticide, plant growth regulator, risk assessment

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SUMMARY

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012 as amended by Commission Implementing Regulation (EU) No 2016/183. Daminozide is one of the active substances listed in that Regulation.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), Czech Republic and co-rapporteur Member State (co-RMS), Hungary, received an application from EU Daminozide Task Force consisting of Arysta LifeScience Great Britain Limited and Fine Agrochemicals Limited, for the renewal of approval of the active substance daminozide.

An initial evaluation of the dossier on daminozide was provided by the RMS in the renewal assessment report (RAR) and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

According to representative uses proposed at EU level, the application of daminozide by spraying as a plant growth regulator on ornamentals (in-field and high-technology permanent greenhouse), results in a sufficient efficacy as plant growth regulator.

The assessment of the data package revealed no issues that could not be finalised or that need to be included as critical areas of concern with respect to **identity, physical–chemical and technical properties** of the active substance and the formulations for representative uses and analytical methods.

As regards **mammalian toxicology and non-dietary exposure**, the original and newly proposed reference specification is not fully supported from the toxicological point of view leading to a critical area of concern. The reliability assessment of key toxicological studies, the potential differences on the formation of relevant metabolites UDMH and NDMA in human metabolism compared to laboratory animal species and the genotoxicity potential of the carcinogenic impurity and hydrolysis product UDMH (including setting of reference values and non-dietary risk assessment) are identified as issues that could not be finalised.

Given that the representative use is only on ornamentals and the potential for **residues** in succeeding crops is low, a dietary consumer risk assessment is generally not required, except for bee products intended destined for human consumption. Due to the absence of data on the magnitude of residues in bee products, it was not possible to assess the relevance of daminozide and UDMH residues in bee's products for the dietary risk to consumers.

In the area of **environmental fate and behaviour** a data gap was identified for information on the effect of water treatment processes on the nature of residues of both the active substance and its metabolite methanol potentially present in surface water, when surface water is abstracted for the production of drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to **ecotoxicology**. The chronic risk assessment for honey bee larvae could not be finalised for the representative ornamental field use.

According to point 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that daminozide is not an endocrine disruptor.

BACKGROUND

Commission Implementing Regulation (EU) No 844/2012,[1] as amended by Commission Implementing Regulation (EU) No 2018/1659,[2] (hereinafter referred to as 'the Regulation'), lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009.[3] This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of an additional 3 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3). Furthermore, in accordance with Article 13(3a), where the information available in the dossier is not sufficient to conclude the assessment on whether the approval criteria for endocrine disruption are met, additional information can be requested to be submitted in a period of minimum 3 months, not exceeding 30 months, depending on the type of information requested.

In accordance with Article 1 of the Regulation, the RMS Czech Republic, and co-rapporteur Member State (co-RMS), Hungary, received an application from EU Daminozide Task Force consisting of Arysta LifeScience Great Britain Limited and Fine Agrochemicals Limited, for the renewal of approval of the active substance daminozide. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Hungary), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on daminozide in the RAR, which was received by EFSA on 31 October 2018 replaced by a later version in July 2019 (Czech Republic, 2019).

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, U Daminozide Task Force consisting of Arysta LifeScience Great Britain Limited and Fine Agrochemicals Limited, for consultation and comments on 24 July 2019. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 25 September 2019. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA, the RMS and the European Chemical Agency (ECHA) on 10 December 2019. 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, environmental fate and behaviour, and ecotoxicology.

In addition, following a consultation with Member States in the Pesticides Peer Review Expert teleconference 16 (15–18 June 2020), it was considered necessary to apply an additional clock stop of 30 month in accordance with Commission Implementing Regulation (EU) No 2018/1659, to be able to conclude whether the approval criteria for endocrine disruption in line with the scientific criteria for the determination of endocrine disrupting properties, as laid down in Commission Regulation (EU) 2018/605,[4] are met.

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

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

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in October–November 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the formulation for representative uses, evaluated on the basis of the representative use of daminozide as a plant growth regulator on ornamentals (field and greenhouse), as proposed by the applicant.

[1]Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.

[2]Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605.

[3]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.

[4]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.

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

A key supporting document to this conclusion is the peer review report (EFSA, 2024), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting tables (10 December 2019 and 11 September 2023[5]);
- the evaluation table (13 December 2024);
- the report(s) of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Czech Republic, 2024), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

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

THE ACTIVE SUBSTANCE AND THE FORMULATION(S) FOR REPRESENTATIVE USES

Daminozide is the ISO common name for *N*-(dimethylamino)succinamic acid (IUPAC).

The formulations for representative uses for the evaluation were 'Alar'and 'Dazide Enhance'both a water soluble granule (SG) containing 850 g/kg and 851.4 g/kg pure daminozide, respectively.

None of the co-formulants present in the formulations for representative uses is listed in Annex III of Regulation (EC) No 1107/2009,[6] nor considered as an active substance in accordance with Regulation (EC) No 1107/2009.

The representative uses evaluated were application as a growth regulator on ornamentals in (high-technology) permanent greenhouses applied via gantry automated and hand-held sprayer, and field applications on ornamentals applied via hand-held sprayer. Full details of the Good Agricultural Practice (GAPs) can be found in the list of end points in Appendix B.

Data were submitted to conclude that the uses of daminozide according to the representative uses proposed at EU level result in a sufficient efficacy as a plant growth regulator, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

CONCLUSIONS OF THE EVALUATION

General aspects

With regard to the mammalian toxicity information available for the formulations for representative uses 'Alar 85 SG' and 'Dazide Enhance SG', studies were performed for acute endpoints. With regard to the co-formulants contained in 'Alar 85 SG', sufficient toxicological data were available for all components but one (present below 10% in the formulation). For this co-formulant, the peer review experts considered that the available toxicological information did not sufficiently address the genotoxicity and repeated dose toxicity potential over the short- and long-term and that they might be considered for further assessment. The collected information (not covering all endpoints), including the existing uses other than plant protection products, under regulated EU frameworks, did not highlight any concern (see Section 10).[7]

With regard to the co-formulants contained in 'Dazide Enhance SG', sufficient toxicological data were available for all components but two (one present in limited amount and the other well below 10% in the final formulation). For these two co-formulants, the experts considered that the available toxicological information did not sufficiently address e.g. the genotoxicity and repeated dose toxicity potential over the short- and long-term and that they might be considered for further assessment. The collected information (not covering all endpoints), including the existing uses other than plant protection products, under regulated EU frameworks, did not highlight any concern (see Section 10).[8]

The availability of ecotoxicity data with the formulation for representative uses was discussed at the experts' meeting[8] and no concern was identified for the co-formulants.

[5]Reporting Table following consultation on the revised RAR on the assessment of the endocrine disrupting properties made available after the clock stop applied in accordance with Commission Regulation (EU) No 2018/1659.

[6]Commission Regulation (EU) 2021/383 of 3 March 2021 amending Annex III to Regulation (EC) No 1107/2009 of the European Parliament and Council listing co-formulants which are not accepted for inclusion in plant protection products. OJ L 74, 4.3.2021, p. 7–26.

[7]Refer to the experts' consultation 2.23 in the Report of the Pesticides Peer Review Experts' Teleconference 124 (EFSA, 2024).

[8]Refer to the experts' consultation 5.6 in the Report of the Pesticides Peer Review Experts' Teleconference 129 (EFSA, 2024).

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

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, 2000b, 2010).

A common reference specification covering all sources was proposed based on batch data from industrial production plants. The proposed minimum purity of the technical material is 990 g/kg. *N*,*N*-dimethylnitrous amide (NDMA) and 1,1-dimethylhydrazine (UDMH) were considered relevant impurities with maximum contents of 1 and 30 mg/kg, respectively (See Section 2). It is proposed to update the original reference specification due to the lower proposed specified level of the relevant impurity NDMA. The original and newly proposed reference specification is not fully supported from the toxicological point of view (see Section 2). The batches used in the ecotoxicological assessment support the newly proposed reference specification but not the original one (see Section 5). A FAO specification was not available for daminozide.

The main data regarding the identity of daminozide and its physical and chemical properties are given in Appendix B. **Data gaps** were identified for solubility of the active substance in aliphatic hydrocarbons and for persistent foaming of the formulation 'Dazide Enhance' at maximum in-use spray concentration (see Section 10).

Adequate analytical methods are available for the generation of data required for the risk assessment, except that related to hazard data used for the toxicological assessment.[9] Although the required information for the methods used in support of toxicological studies was provided by the applicant, it was not assessed by the RMS and not included in the RAR, so therefore was not peer reviewed (data gap, see Section 9.1). Methods of analysis are available for the determination of the active substance and relevant impurities in the technical material and in the representative formulations and for the determination of the impurities in the technical material. However, a confirmatory method for the determination of the relevant impurities in both formulations is missing (data gap, see Section 10).

Residue definitions for monitoring in food/feed of plant origin is proposed to be daminozide and UDMH, expressed as daminozide (see Section 3), therefore a data gap for a monitoring method in food/feed of plant origin was identified (See Section 10). An analytical method for monitoring in food/feed of animal origin is not required since a residue definition for monitoring in animal products was not proposed (see Section 3).

Daminozide residue in soil and water can be monitored by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with LOQs 0.05 mg/kg and 0.1 µg/L respectively. Appropriate LC–MS/MS method exists for monitoring of daminozide and UDMH residues in air with LOQs of 1.67 µg/m^3 and 0.025 µg/m^3, respectively. LC–MS/MS can be used for monitoring of daminozide and UDMH residues in body fluids and tissues with LOQs of 0.01 mg/L (expressed as daminozide) and 0.01 mg/kg (expressed as daminozide).

2 | MAMMALIAN TOXICITY

The toxicological profile of the active substance **daminozide** and its metabolites was discussed at the Pesticides Peer Review Teleconference 16, in June 2020 and Teleconference 124 and 125 in January 2024. The assessment is based on the following guidance documents: European Commission (2003) and EFSA (2017).

The original and newly proposed reference specifications (see Section 1) are not fully supported from a toxicological point of view, leading to **a critical area of concern** (see Section 9.2). In this respect, UDMH (with inconclusive genotoxicity assessment[10] and harmonised classification as carcinogen category 1B (ATP 00)[11]) and NDMA (with harmonised classification as carcinogen category 1B (ATP 00)[11]) were identified as relevant impurities. According to EFSA, the maximum content of 2 mg/kg for NDMA (proposed to be maintained by the applicant) should be lowered to 1 mg/kg based on European Commission (2003). The maximum level of 2 mg/kg should be further substantiated.[12] As regards UDMH, according to the RMS the maximum content of 30 mg/kg for UDMH can be supported from a toxicological point of view based on the margin of exposure (MoE) approach. EFSA considered setting an acceptable maximum content for UDMH as an issue that could not be finalised (see Section 9.1).

Based on available information in the RAR, EFSA could not conclude whether the analytical methods used in feed, body fluids and tissues, air and any additional matrices used in support of the toxicity studies and non-dietary exposure are considered fit-for-purpose (see Section 1) leading to a data gap and an issue that could not be finalised (see Section 9.1).

[9]See data requirement 1.10 in the evaluation table (EFSA, 2024).

[10]Genotoxicity data considered for classification and labelling are not available to EFSA.

[11]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, Annex VI.

[12]EFSA noted that EFSA CONTAM Panel derived a BMDL10 of 0.01 mg/kg bw per day for various nitrosamines including NDMA (EFSA CONTAM Panel, 2023).

The oral **absorption** of daminozide is estimated to account for ca. 38% of the administered low dose. **Excretion** occurs predominantly through the faecal route, with appreciable amounts excreted in urine. Daminozide is widely **distributed** with the highest levels being reached in liver. There was no evidence of **accumulation**. Daminozide appears to be largely metabolised to UDMH. Comparative in vitro metabolism study was not conclusive regarding the formation of UDMH and NDMA in human metabolism and a data gap and issue that could not be finalised were identified (see Section 9.1). Toxicokinetic parameters, such as Cmax, Tmax and plasma t1/2, were not determined leading to a data gap (see Section 10). The **residue definition** for body fluids and tissues includes daminozide and UDMH.

Daminozide has low acute toxicity by oral, dermal and inhalation exposure and has no skin irritating properties. Daminozide was shown to be mildly irritating to the eyes and there is no clear evidence that demonstrates skin sensitising potential of daminozide. Daminozide has not harmonised classification and labelling for eye irritation and skin sensitisation (ECHA, 2020 and ATP 18[11]).

Short-term oral toxicity studies were provided for rats and dogs. The adverse effects included decreased body weight gain (rat and dogs) and clinical signs (food-like emesis, soft stool in dogs). The rat was the most sensitive species with a no observed adverse effect level (NOAEL) of 40 mg/kg bw per day (90-day study).

Based on the available **genotoxicity** data package and weight of evidence approach, daminozide is unlikely to be genotoxic.

Based on its ultraviolet–vis (UV–vis) spectra, phototoxicity and photomutagenicity testing is not required for daminozide.

After **long-term oral exposure**, target organs included lungs in mice and bile duct and ovaries in rats. The rat was the most sensitive species with a lowest observed adverse effect level (LOAEL) of 5 mg/kg bw per day (2-year study, no NOAEL was identified) for systemic toxicity. Daminozide has harmonised classification and labelling as carcinogenic category 2 H351 (ECHA, 2020 and ATP 18[11]; lung tumours reported in male and female mice as well as the uterine tumours in female rats are considered relevant for carcinogenicity classification). The carcinogenicity LOAEL is 45 mg/kg bw per day (2-year, mice study; no NOAEL identified).

With regard to **reproductive toxicity** studies, fertility and overall reproductive performance were not affected. In the multigeneration rat study (gavage), the relevant parental NOAEL is 360 mg/kg bw per day based on clinical signs and increased water consumption. The offspring and reproductive toxicity NOAEL is 1200 mg/kg bw per day, the highest dose level tested. In the multigeneration rat study (diet) diet, the relevant parental NOAEL is 50 mg/kg bw per day based on body weight changes. The offspring and reproductive toxicity NOAEL is 500 mg/kg bw per day, the highest dose level tested.

With regard to foetal development, slight reduction in ossification, decreased fetal weight and abortions were observed in rabbit with a developmental NOAEL of 500 mg/kg per day, whereas the maternal NOAEL is 250 mg/kg bw per day based on mortality and clinical signs. In the rat teratogenicity study, the maternal NOAEL is 150 mg/kg bw per day based on reduced body weight gain, and the developmental NOAEL is 1500 mg/kg bw per day, the highest dose level tested.

With respect to **neurotoxicity**, decreased locomotor activity (basic and fine movement, total distance) was observed in the acute neurotoxicity study in rats, triggering a NOAEL of 1000 mg/kg bw. In the 90-day neurotoxicity study, the NOAEL for neurotoxicity was 1000 mg/kg bw per day, the highest dose level tested.

As regards **immunotoxicity**, daminozide was not immunotoxic in the 28-day mouse study.

The **acceptable daily intake** (**ADI**) is 0.017 mg/kg bw per day, based on the 2-year rat study in which a LOAEL of 5 mg/kg bw per day was set based on ovarian atrophy and cysts and bile duct hyperplasia in rats. Since a NOAEL was not identified, an additional UF of 3 plus the standard uncertainty factor (UF) of 100 was applied. This value differs from the one set in the previous daminozide peer review where the ADI of 0.45 mg/kg bw per day was based on a 2-year mouse study applying an UF of 100 (European Commission, 2005).

The **acceptable operator exposure level** (**AOEL**) is 0.0063 mg/kg bw per day, based on the 2-year rat study in which a LOAEL of 5 mg/kg bw per day was set based on ovarian atrophy and cysts and bile duct hyperplasia in rats. Since a NOAEL was not identified, an additional UF of 3 plus the standard uncertainty factor (UF) of 100 was applied, as well as a correction factor for limited oral absorption of 38%. This value differs from the one set in the previous daminozide peer review where the AOEL of 0.16 mg/kg bw per day was based on 2-year, mouse, study applying an UF of 100 (European Commission, 2005).

The **acute reference dose** (**ARfD**) and **acute AOEL** (**AAOEL**) are not necessary based on the toxicological profile of the active substance. During the previous peer review an ARfD was not set (European Commission, 2005).

Non-dietary exposure considered the representative uses with 'Alar 85 SG' and 'Dazide Enhance SG' as plant growth regulators in ornamentals.

UDMH is a hydrolysis product (it is formed in the spray tank, i.e. 3.75 g daminozide produced 3.7 mg UDMH over 24 h; 4.19–7.55 g UDMH/ha), a relevant impurity and a mammalian metabolite of daminozide. The experts agreed that the genotoxic potential of UDMH (including aneugenicity) could not be concluded based on the available in vitro and in vivo data[13] and a data gap was identified leading to an issue that could not finalised (see Section 9.1). Therefore no reference values could be set[14] leading to an issue that could not be finalised.

Dermal absorption of daminozide in the representative product Alar 85 SG has been assessed in an in vitro study with human skin. Based on the EFSA guidance (EFSA, 2017), the dermal absorption values are 0.26% for the concentrate (425 g/kg), 1.6% for the 8.5 g daminozide/L spray dilution and 2.6% for the 0.2125 g daminozide/L spray dilution.

[13]Refer to the experts' consultation 2.14 in the Report of the Pesticides Peer Review Experts' Teleconference 16 (EFSA, 2024).

[14]The RMS presented non-dietary exposure to UDMH considering the margin of exposure (MoE). In this respect, it is noted that it is up to risk managers to decide on whether a MoE is acceptable for a (potential) genotoxic and carcinogenic metabolite under the EU pesticide regulatory framework. Please refer to the experts' consultation 2.20 in the Report of the Pesticides Peer Review Experts' Teleconference 16 (EFSA, 2024).

Dermal absorption of daminozide in the representative product Dazide Enhance SG has been assessed in an in vitro study with human skin. Based on the EFSA guidance (EFSA, 2017), the dermal absorption values are 0.2% for concentrate, 1.9% for spray dilution (5.1 g/L) and 1.2% for spray dilution (0.425 g/L).

The exposure estimates[15] considered automated and hand-held application in indoor scenarios and hand-held application in outdoor. The EFSA model, either 2014 or 2022 is not applicable to the dossier on daminozide because the application was submitted before 1st of January 2016. However, the results according to EFSA 2014 as reported by the RMS in the assessment report together with applicable models are mentioned below.

For daminozide, as regards automated application, **operator** exposure is below the AOEL without the use of personal protective equipment (PPE) according to the applicable and available (UK POEM, German and EFSA) models (only mixing and loading was considered[16]).

For hand-held application, indoor or outdoor operator exposure to daminozide is above the AOEL even with the use of PPP (respiratory protective equipment, FFP2) according to available (including EFSA model) and applicable models (Dutch or UK POEM, for indoor and outdoor uses).[17]

For the re-entry activities such as handling ornamentals, **worker** exposure is below AOEL (97% of the AOEL for 'Alar 85 SG' considering an 8-days re-entry interval and 98% of the AOEL for 'Dazide Enhance SG' considering a 4–7 days re-entry interval) if they use PPE (gloves and respiratory protective equipment) according to the German model and considering refinements of DFR and DT50 obtained from a field study.

For inspection, exposure is below the AOEL without the use of PPP but considering a 4 and 3-days re-entry interval for 'Alar 85 SG' and 'Dazide Enhance SG', respectively and according to the German model.

Bystander and resident exposure were estimated according to the German model for hand-held application, outdoors uses. This scenario was considered the worst case for the intended representative uses.[18] Bystander and resident exposure to daminozide is below the AOEL (buffer strip of 10 meter and two instead of five applications). According to the EFSA model (either 2014 or 2022) resident children exposure is above the AOEL for both 'Alar 85 SG' and 'Dazide Enhance SG'.

Methanol (M1) can occur in groundwater above 0.1 but below 0.75 µg/L in 1/7 scenarios in greenhouse uses (see Section 4). EFSA noted that experimental genotoxicity studies have not been submitted by the applicant (data gap); the RMS referred to REACH registration dossier.[19] Methanol has harmonised classification as toxic if swallowed, in contact with the skin and if inhaled (acute tox. 3) and can cause damage to organs (STOT SE 1), based on this methanol is a relevant groundwater metabolite. However, this is not leading to a critical area of concern since it represents only 1/7 scenarios for one use.

3 | RESIDUES

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

Metabolism studies in plants were not available because the representative use is on ornamentals, which are neither food nor feed items. However, it is noted that from Joint Meeting Pesticides Residues (FAO, 1977),[20] there are indications that daminozide degrades in plants to unsymmetrical dimethylhydrazine (UDMH), which is classified as a carcinogenic metabolite with inconclusive genotoxicity (see Section 2). In the soil, daminozide degrades quickly (see Section 4), and the transfer of significant residues to rotated crops is not expected when ornamentals are grown in rotation with crops for human consumption. Nevertheless, considering that studies are not available and that plant residues related to a use in ornamentals could be relevant for bee products, the **plant residue definitions** for enforcement and risk assessment previously proposed by EFSA (EFSA, 2012) remain unchanged as daminozide and UDMH, expressed as daminozide.

Although no guidance was available at the date of dossier's submission, since the ornamentals could be visited by bees, the determination of residues in bee products for human consumption is needed and was not available (data gap, see Section 10). Without such data, it was not possible to assess the possible transfer of daminozide and UDMH metabolite residues to bee products.

Consequently, a dietary consumer risk assessment with regard to bee products for human consumption cannot be performed. In addition, the consumer risk assessment could not be finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain the active substance and its metabolites (see Sections 4 and 9.1).

[15]The RMS also performed calculations according to the EFSA AOEM model, when applicable. However, this model was not applicable at the time of submission of the dossier and the results are provided in the revised RAR only (see Volume 3 CP, B.6, Czech Republic, 2024).

[16]According to the EFSA non-dietary guidance lacking data on e.g. cleaning and maintenance of equipment, exposure on mixing/loading alone is likely to underestimate operator exposure.

[17]The RMS also applied the Southern European Glasshouse model; however, this was not an accepted model at EU level.

[18]For indoor uses, exposure pathway was limited to vapour, since even in high-technology permanent greenhouses, ventilation systems cannot prevent air exchanges. However, according to the EFSA model 2022 the only exposure pathway that should be excluded for bystanders/residents for indoor uses is re-entry, therefore calculations according to German model could be underestimated according to the current state of the art. It is also noted that the German model considered two instead of five applications as it would be recommended using the EFSA model 2022.

[19]https://chem.echa.europa.eu/100.000.599/overview?searchText=methanol.

[20]https://www.inchem.org/documents/jmpr/jmpmono/v077pr17.htm.

It is highlighted that during the renewal process the toxicological reference values were lowered. Although no exceedance of the ADI and ARfD from the existing EU-MRLs are expected, due to high toxicological concern on UDMH, residues of daminozide should not be present in food or feed items.

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

Daminozide was discussed at the Pesticides Peer Review Teleconference 18 in June 2020.

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, daminozide exhibited very low persistence, forming the major (> 10% applied radioactivity (AR)) metabolite methanol (max. 27% AR), which exhibited low persistence. Mineralisation of the dimethylamino ^{14}C radiolabel to carbon dioxide accounted for 58%–68% AR after 62 days. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for 23%–33% AR after 62 days. The anaerobic degradation and soil photolysis of daminozide were not significant routes of degradation. Daminozide exhibited very high mobility in soil. Metabolite methanol exhibited very high mobility in soil according to the estimation done using the QSAR tool (KOCWIN v2.0 using both the MCI and LogKow methods). The report on the use of QSAR tools to estimate the adsorption endpoints for metabolite methanol was not provided (**data gap**, see Section 10). It was concluded that the adsorption of daminozide was not pH dependent. Field dissipation studies were not performed as daminozide exhibited very low persistence in soil.

The available laboratory incubations in dark aerobic natural sediment water systems were considered not acceptable (**data gap**, see Section 10). However, during the Pesticides Peer Review Teleconference 18 experts agreed that the available degradation endpoints for daminozide derived from the not acceptable incubations might be used pending any future provision of a more appropriate study. Exceptionally, EFSA agreed to this approach in this case, considering the supporting information on degradation endpoints from the available aerobic mineralisation study. Daminozide was stable in a laboratory sterile aqueous photolysis experiment. The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for daminozide and metabolite methanol using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance daminozide and metabolite methanol, appropriate step 3 (FOCUS, 2001) calculations were available.

For the representative protected use, the necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC)) were appropriately carried out using the FOCUS (2001) step 1 and step 2 approach (3.2 of the steps 1–2 in FOCUS calculator), which was then modified by post processing the spray drift input results (option no runoff or drainage was selected) to obtain a 0.2% emission of daminozide from greenhouses being re-deposited on adjacent surface water bodies, which is appropriate when applications are made with ultra-low volume application techniques. This approach has been accepted by Member State experts as an assumption that can be used in EU level surface water exposure assessments for greenhouse uses and is referred to in FOCUS (2008) guidance as being appropriate.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[21] During the Pesticides Peer Review Teleconference 18 experts agreed that the simulation results using PELMO should not be relied on for methanol as PELMO did not simulate volatilisation in the soil column for metabolites. The potential for groundwater exposure from the representative uses by daminozide 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. Only for the representative uses in greenhouse (permanent structures) for ornamentals above 50 cm, methanol 80th percentile annual average concentrations moving below 1-m depth were predicted to be above the parametric drinking water limit of 0.1 µg/L in 1 out of 7 scenarios of the pertinent FOCUS groundwater scenarios. For the representative uses in field for ornamentals up to and below 50 cm and in greenhouse (permanent structures) for ornamentals up to 50 cm, methanol 80th percentile annual average concentrations moving below 1-m depth were predicted to be below the parametric drinking water limit of 0.1 µg/L in seven out of seven scenarios. Based on the information available in the mammalian toxicity section, this metabolite is considered relevant for human health (see Section 2).

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 Sections 3 and 9.1).

The volatile metabolite methanol will be subject to long-range atmospheric transport. The applicant made the case that the quantity of methanol originating from uses of daminozide, will be insignificant in comparison to that produced by other anthropogenic activity or its natural production during natural organic matter turnover and degradation. This case was assessed as valid.

The PEC 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 C of this conclusion.

[21]Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

5 | ECOTOXICOLOGY

The risk assessment was based on the following documents: European Commission (2002a, 2002b), SETAC (2001), EFSA (2009, 2013) and EFSA PPR Panel (2013).

Daminozide was discussed at the Pesticide peer-review teleconferences 21 (July 2020) and teleconference 129 (January and February 2024).

The batches used in the ecotoxicological assessment support the newly proposed reference specification but not the original one.

The two formulations for the representative uses, 'Alar' and 'Dazide Enhance', have been considered ecotoxicologically comparable. Therefore, in the absence of specific endpoints with one of these formulations, it has been deemed acceptable to perform the risk assessment using the endpoint from the other formulation.

The applicant confirmed that the greenhouse uses are restricted to high-technology permanent structures. For this representative use, low risk to birds and mammals, bees, non-target arthropods other than bees, soil organisms and non-target terrestrial plants was concluded based on minimal exposure (EFSA, 2015) and, in the case of soil organisms, also that daminozide and its metabolite methanol are not persistent in soil (see Section 4).

For daminozide, suitable toxicity data were available for the acute and long-term assessment of **birds** and **wild mammals**. Additionally, acute studies with both formulations for representative uses were available for mammals. The tier 1 risk assessment indicated low acute risk to birds and high long-term risk to birds and high acute and long-term risk to mammals for the field use. The experts discussed several options to refine the risk assessment for terrestrial vertebrates. Refined interception values were accepted for several BBCH stages. The refined risk assessment did not change the outcome of the tier 1 risk assessment. Low risk to birds and mammals from secondary poisoning and from exposure to contaminated water was concluded for the field use of daminozide. Low risk to the relevant metabolite methanol was also concluded.

For the risk assessment of **aquatic organisms**, suitable acute and chronic toxicity data were available with daminozide for fish, aquatic invertebrates and algae. Furthermore, studies with both formulations for the representative uses were submitted for fish (acute), aquatic vertebrates (acute) and algae. A study with formulation 'Alar' and aquatic macrophytes was also available. Considering the available data and risk assessment, low risk was concluded for the field (at FOCUSsw Step 2) and greenhouse uses in ornamentals. A screening risk assessment was presented for the relevant metabolite methanol assuming the metabolite to be 10 times more toxic than the active substance. Low risk to methanol was indicated for all aquatic taxa and for all representative uses at FOCUSsw Step 3.

Acute (oral and contact) studies with honey **bees** were available with the formulation for representative uses 'Alar'. Chronic toxicity data with the active substance was only available for adult bees. The experts considered that the available larval study was not valid and, thus, it was not used for the risk assessment. Low acute risk from oral and contact exposure was concluded using the European Commission (2002a) and EFSA (2013) assessment schemes for the field uses in ornamentals. High chronic risk to adult bees was indicated for the 'treated crop' and 'flowering weeds' scenarios. In the absence of a valid endpoint, the risk assessment for honey bee larvae could not be finalised (**data gap**; see Section 9.1). Low risk to metabolite methanol was concluded. A suitable assessment for accumulative and sub-lethal effects was not available (**data gap** for sub-lethal effects, see Section 10). No studies with bumble bees and solitary bees were submitted.

For **non-target arthropods** other than bees, tier 1 (glass plate) and/or extended laboratory studies with the standard species *Aphidius rhopalosiphi* and *Typhlodromus pyri* and with the additional species *Chrysoperla carnea*, *Encarsia formosa*, *Orius laevigatus* and *Poecilus cupreus* were available with the active substance and/or with the formulations for the representative uses. Low in-field and off-field risk was concluded for the field uses of daminozide.

A chronic **earthworm** study was available with the active substance, while studies with the formulation for representative uses 'Alar' and the soil **macro-organisms** *Folsomia candida* and *Hypoaspis aculeifer* were submitted. Considering the studies and the outcome of the tier 1 risk assessment, a low risk to all soil macro-organisms was concluded for the field uses in ornamentals. The risk assessment for the metabolite methanol was covered by the risk assessment of the parent substance. A low risk to **soil microorganisms** was also concluded for daminozide and the relevant metabolite methanol in field uses in ornamentals.

Based on the available data, a low risk was concluded for **non-target terrestrial plants** and organisms involved in **biological methods for sewage treatment**.

6 | ENDOCRINE DISRUPTION PROPERTIES

The endocrine disruption properties of daminozide were discussed at the Pesticides Peer Review Teleconference 16, in June 2020 and Pesticides Peer Review Experts' teleconferences (TCs) 124 and 125 (joint session mammalian toxicology and ecotoxicology, 30 January 2024).

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

With regard to the assessment of the endocrine disruption potential of daminozide for humans according to the ECHA/EFSA guidance (2018), for T-modality, the ED criteria are not met because there is no T-mediated pattern of adversity in a complete dataset (Scenario 1a applies). For EAS-modalities, level 2 and 3 studies were made available and they are acceptable and negative. ED criteria are not met for daminozide because no endocrine activity has been observed for the EAS-modalities. Therefore, the dataset for the EAS-modalities is considered complete and the applicable scenario is Scenario 2a (ii). Overall, the ED criteria for EATS-modalities are not met.

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**.

For non-target organisms other than mammals, a Xenopus Eleutheroembryonic thyroid assay (XETA) and a Fish short-term reproduction assay (FSTRA) were available to sufficiently investigate the endocrine activity through the T- and EAS-modalities, respectively. Both studies were valid and fully reliable. No positive evidence of endocrine activity was observed in those studies.

According to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that daminozide is not an endocrine disruptor.

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
Daminozide	Low risk to soil organisms
Methanol	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
Daminozide	No	Yes	–	–	Yes
Methanol	Yes, but only for ornamentals above 50 cm in greenhouse (permanent): 1/7 FOCUS scenarios (0.180 µg/L)	Data gap	Yes Harmonised classification as toxic if swallowed, in contact with the skin and if inhaled (acute tox. 3) and can cause damage to organs (STOT SE 1) (genotoxicity studies not submitted)	No	Open for a full assessment. Relevant based on harmonised classification and labelling.

[a]Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).

[b]FOCUS scenarios or relevant lysimeter. Ranges indicated for FOCUS scenarios include the result from the model giving the highest concentration at each scenario, as needed to comply with European Commission (2014a, 2014b) guidance.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Daminozide	Low risk to aquatic organisms
Methanol	Low risk to aquatic organisms

TABLE 4 Air.

Compound (name and/or code)	Toxicology
Daminozide	Low acute toxicity by inhalation (Rat LC50 inhalation > 2.1 mg/L air/4 h)
Methanol	Harmonised classification as toxic if inhaled (acute tox. 3) The quantity of methanol originating from uses of daminozide, will be insignificant in comparison to that produced by other anthropogenic activity or its natural production during natural organic matter turnover and degradation

8 | PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT BY RISK MANAGERS

Risk mitigation measures (RMMs) identified following consideration of Member State (MS) and/or applicant's proposal(s) during the peer review, if any, are presented in this section (Table 5). 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 concerned 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.

	Ornamentals		
Representative use	**G Gantry automated**	**G Hand-held application**	**F Hand-held application**
Operator risk	None.	Not applicable. Risk identified.	Not applicable. Risk identified.
Worker exposure	Use of PPE and re-entry interval is required[a]	Use of PPE and re-entry interval is required[a]	Use of PPE and re-entry interval is required[a]
Bystander/resident exposure	10 m buffer	10 m buffer	10 m buffer

[a]For the re-entry activities such as handling ornamentals, gloves and respiratory protective equipment according to the German model. For 'Alar 85 SG' considering an 8-days re-entry interval and 98% of the AOEL for 'Dazide Enhance SG' considering a 4–7 days re-entry interval. For inspection, exposure is below the AOEL without the use of PPP but considering a 4 and 3-days re-entry interval for 'Alar 85 SG' and 'Dazide Enhance SG', respectively and according to the German model.

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[22] 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. Reliability of key toxicological studies (e.g. those used for setting reference values) could not be fully assessed.

    a. Description and validation data of the methods in support of toxicological studies was provided by the applicant, however a transparent assessment of the provided information by the RMS is missing in the RAR and is not peer-reviewed (relevant for all representative uses evaluated; see Section 1 and 2).

2. Potential differences on the formation of relevant metabolites UDMH and NDMA in human metabolism compared to laboratory animal species.

    a. Comparative in vitro metabolism study with HepaRG cells or plated hepatocytes with long incubation time and different sampling times (e.g. 6–12–24 h).

[22]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.

3. The genotoxicity potential of the carcinogenic impurity and hydrolysis product UDMH is inconclusive.

   a. As an impurity in the reference specification, an acceptable maximun content cannot currently set. Further genotoxicity assessment of UDMH including a new in vitro test battery OECD guideline and GLP-compliant (Ames test and in vitro micronucleus test) with UDMH of known purity (and protected against oxidation). The in vitro test battery could also include a gene mutation mammalian cell test with TK gene. The studies as outlined in the EFSA PPR Panel scientific opinion (EFSA PPR Panel, 2004), and in the REACH dossier[23] should also be included for completeness of the weight of evidence assessment.
   b. As a hydrolysis product formed from daminozide when it is added to water (i.e. during application), setting of reference values (e.g. AOEL) cannot currently set, leading to an inconclusive risk assessment.

4. The consumer risk assessment could not be finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment following abstraction of surface water that might contain the active substance and its metabolites (see Sections 3 and 4).

   a. Further data and information were not available to demonstrate that residues of daminozide and methanol will have no immediate or delayed harmful effects on human health, including that of vulnerable groups, or animal health, through drinking water (taking into account substances resulting from water treatment (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).

5. The chronic risk to bee larvae could not be finalised.

   a. A valid bee larval study was not available (for the representative field use to ornamentals (see Section 5).

9.2 | Critical areas of concern

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

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

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

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:

6. The original and newly proposed reference specification is not fully supported from the toxicological point of view

   a. The proposed maximum content for the relevant carcinogenic impurity NDMA is 2 mg/kg, however, according to European Commission (2003) the acceptable level for N-nitrosamines should not exceed 1 mg/kg. Therefore, the case for keeping the level at 2 mg/kg should be further substantiated (relevant for all representative uses evaluated; see Section 2).

9.2.1 | 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 7, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

In addition to the issues indicated in Table 6 below, the reference specification proposed was not comparable to the material used in the testing that was used to derive the toxicological reference values.

[23] https://chem.echa.europa.eu/100.000.287/overview.

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.

		Ornamentals		
		Greenhouse		Field
Representative use		Automated	Hand-held	Hand-held
Operator risk	Risk identified		X[a]	X[a]
	Assessment not finalised	X[d]	X[d]	X[d]
Worker risk	Risk identified			
	Assessment not finalised	X[d]	X[d]	X[d]
Resident/bystander risk	Risk identified			
	Assessment not finalised	X[d]	X[d]	X[d]
Consumer risk	Risk identified			
	Assessment not finalised			
Risk to wild non-target terrestrial vertebrates	Risk identified			X
	Assessment not finalised			
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified			X[c]
	Assessment not finalised			X[5]
Risk to aquatic organisms	Risk identified			
	Assessment not finalised			
Groundwater exposure to active substance	Legal parametric value breached			
	Assessment not finalised			
Groundwater exposure to metabolites	Legal parametric value breached[b]		1/7 FOCUS scenarios	
	Parametric value of 10 µg/L breached			
	Assessment not finalised			

Notes: 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, 4 and 7 for further information.

[a]For hand-held application, indoor or outdoor operator exposure to daminozide is above the AOEL even with the use of PPP (respiratory protective equipment, FP2) according to available models (see Section 2).

[b]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.

[c]High chronic risk to adult bees based on EFSA (2013).

[d]Assesment not finalised for non-dietary exposure to UDMH.

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:

- For one of the components of the formulation(s) for representative uses 'Alar 85 SG', e.g. genotoxicity and repeated dose toxicity information over the short- and long-term was not available; therefore, in order to allow a final conclusion on the safety assessment of 'Alar 85 SG', e.g. genotoxicity and repeated dose toxicity data for this/these component(s) (short- and long-term) might be considered for further assessment (to be confirmed by Member States when assessing applications for PPP authorisation; relevant for all representative uses evaluated; see Section 'General aspects').
- For two of the components of the formulation(s) for representative uses 'Dazide Enhance SG', e.g. genotoxicity and repeated dose toxicity information over the short- and long-term was not available; therefore, in order to allow a final conclusion on the safety assessment of 'Dazide Enhance SG', e.g. genotoxicity and repeated dose toxicity data for this/these component(s) (short- and long-term) might be considered for further assessment (to be confirmed by Member States when assessing applications for PPP authorisation; relevant for all representative uses evaluated; see Section 'General aspects').
- A search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health and published within the 10 years before the date of submission of the dossier, in accordance with EFSA (2011) (relevant for all representative uses evaluated; see Section General aspects).
- Solubility of the active substance in aliphatic hydrocarbons (relevant for all representative uses evaluated; see Section 1).

- Persistent foaming of the formulation 'Dazide Enhance' at maximum in-use spray concentration (relevant for all representative uses evaluated; see Section 1).
- A confirmatory method for the determination of the relevant impurities in both formulations for representative uses (relevant for all representative uses evaluated; see Section 1).
- Monitoring method(s) for all components of the residue definition for monitoring in food/feed of plant origin including bee products for human consumption (relevant for all representative uses evaluated; see Section 1).
- Screening for biological activity of methanol according SANCO/221/2000-rev.10-final Step 3 a Stage 1 (relevant for greenhouse uses, see Section 4 and Table 2)
- Toxicokinetic parameters, such as Cmax, Tmax and plasma t1/2, to be determined (relevant for all representative uses evaluated; see Section 2).
- Experimental genotoxicity studies on the groundwater metabolite methanol as described in the European Commission guidance on relevance of groundwater metabolites (relevant for greenhouse uses evaluated; see Sections 2 and 4).
- Sufficient residue trials in honey and other bee's products relevant for human consumption analysed for the residues according to the risk assessment residue definition and covered by storage stability and validated analytical method (relevant for the field use on ornamentals evaluated see Section 3)
- The report on the use of QSAR tools to estimate the adsorption endpoints for methanol (relevant for all representative uses evaluated; see Section 4).
- Laboratory incubations in dark aerobic natural sediment water systems (relevant for all representative uses evaluated; see Section 4).
- Further data were not available to address the risk to honey bees from sub-lethal effects (relevant for the field use, see Section 5).

ABBREVIATIONS

AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
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
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification
MRL	maximum residue level
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PEC	predicted environmental concentration
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation of Chemicals Regulation
SFO	single first-order
SMILES	simplified molecular-input line-entry system
TK	technical concentrate
WHO	World Health Organization

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APPENDIX A

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

Properties		Conclusion[a]
CMR	Carcinogenicity (C)	Daminozide is classified as carcinogen category 2 from: Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: CLP00, and proposed classification according to ECHA RAC opinion (ECHA, 2020; ATP 18[11])
	Germ cell Mutagenicity (M)	Daminozide is not classified as mutagen category 1A or 1B from: Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: CLP00, and proposed classification according to ECHA RAC opinion (ECHA, 2020; ATP 18[11])
	Toxic for Reproduction (R)	Daminozide is not classified as reproduction category 1A or 1B from: Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended]: CLP00, and proposed classification according to ECHA RAC opinion (ECHA, 2020; ATP 18[11])
Endocrine disrupting properties		Daminozide is not considered to meet the criteria for endocrine disruption for human health and non-target organisms according to points 3.6.5 and 3.8.2 of Annex II of Regulation No 1107/2009, as amended by Commission Regulation (EU) 2018/605.
POP	**Persistence** **Bioaccumulation** **Long-range transport**	Daminozide is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
PBT	**Persistence** **Bioaccumulation** **Toxicity**	Daminozide 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.
vPvB	**Persistence** **Bioaccumulation**	Daminozide 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.

[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 formulation for representative uses

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2025.9210.

APPENDIX C

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[24] or not normalised DT_{50} for field studies (SFO equivalent, when biphasic, the DT_{90} was divided by 3.32 to estimate the DT50 when deciding on the wording to use)
Very low persistence	< 1 day
Low persistence	1 to < 10 days
Moderate persistence	10 to < 60 days
Medium persistence	60 to < 100 days
High persistence	100 days to < 1 year
Very high persistence	A year or more

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.

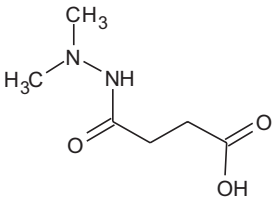
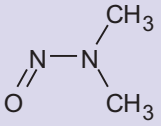
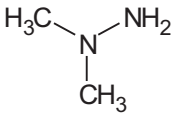
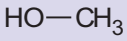
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2000
Slight mobility	2001–5000
Immobile	> 5000

Note: Based on McCall et al. (1980).

[24] 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.

APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
daminozide	*N*-(dimethylamino)succinamic acid O=C(NN(C)C)CCC(O) = O NOQGZXFMHARMLW-UHFFFAOYSA-N	
NDMA	*N*,*N*-dimethylnitrous amide O=NN(C)C UMFJAHHVKNCGLG-UHFFFAOYSA-N	
UDMH	1,1-dimethylhydrazine NN(C)C RHUYHJGZWVXEHW-UHFFFAOYSA-N	
Methanol	methanol OC OKKJLVBELUTLKV-UHFFFAOYSA-N	

[a]The name in bold is the name used in the conclusion.

[b]ACD/Name 2023.2.4 ACD/Labs 2023.2.4 (File Version N25E41, Build 137185, 31 January 2024).

[c]ACD/ChemSketch 2023.2.4 ACD/Labs 2023.2.4 (File Version C45H41, Build 137010, 18 January 2024).