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CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, The Netherlands for the pesticide active substance bixlozone 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 bixlozone as an herbicide on winter cereals (wheat and barley), winter oilseed rape and maize via soil broadcast spray application in field. 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

Bixlozone, herbicide, peer review, pesticide, risk assessment

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CONTENTS

SUMMARY

Bixlozone 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), The Netherlands, received an application from FMC International Switzerland Sàrl on 2 July 2018 for approval. In addition, in accordance with Article 8(1)(g) of the Regulation, FMC International Switzerland Sàrl, submitted an application for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 28 August 2018.

An initial evaluation of the dossier on bixlozone 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 bixlozone according to the representative uses (broadcast soil spray application in field) as an herbicide on winter cereals (wheat and barley), winter oilseed rape and maize, as proposed at EU level result in a sufficient herbicidal efficacy against the target weeds.

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 bixlozone or the representative formulations and **analytical methods**.

In the section of **mammalian toxicity**, due to insufficient information for the assessment of the toxicological relevance of one impurity, its proposed maximum level and the representativeness of the batches used in the toxicological assessment with regard to the proposed reference specification could not be finalised.

In the section of **residues**, the finalisation of the consumer dietary risk assessment considering representative uses is pending due to data gaps on natural occurrence and toxicological information of some metabolites.

The MRL requests were supported by the available data. However, data gaps were identified for the MRLs that have to be established as a consequence of positive residue levels in rotational crops.

In the section of **environmental fate and behaviour** a data gap was identified for information on the effect of chlorination water treatment process on the nature of residues of both the active substance and its identified metabolites that might be present in surface water and/or groundwater when abstracted for the production of drinking water. This data gap led to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses.

In the section of **ecotoxicology**, 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. A high risk to aquatic organisms was indicated for all representative uses other than the use to maize. A low chronic risk to bees could not be concluded for any of the representative uses.

With regard to the **endocrine disruption** (ED) properties, based on the available data and assessment, it can be concluded that bixlozone does not meet the ED criteria for human and non-target organisms 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.

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).

Bixlozone is a new active substance for which, in accordance with Article 7 of the Regulation, the RMS, The Netherlands, received an application from FMC International Switzerland Sàrl on 02 July 2018 for approval of the active substance bixlozone. In accordance with Article 8(1)(g) of the Regulation, FMC International Switzerland Sàrl submitted an application for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005.[2] Complying with Article 9 of the Regulation, the completeness of the dossier was checked by the RMS and the date of admissibility of the application was recognised as being 28 August 2018.

The RMS provided its initial evaluation of the dossier on bixlozone in the DAR, which was received by EFSA on 31 August 2021 (The Netherlands, 2021). The DAR included a proposal to set MRLs, in accordance with Article 11(2) of the Regulation. The peer review was initiated on 14 June 2022 by dispatching the DAR to the Member States and the applicant, FMC International Switzerland Sàrl, 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 teleconference between EFSA, the RMS and ECHA on 25 October 2022. 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.

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.

In accordance with Article 12 of the Regulation, EFSA should adopt a conclusion on whether bixlozone 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 and on the proposed MRLs took place with Member States via a written procedure in September 2024.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the formulation for representative uses evaluated on the basis of the representative uses of bixlozone as a herbicide on winter cereals (wheat and barley), winter oilseed rape and maize 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, if any, are presented in the conclusion.

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

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 DAR;
- the reporting table (27 October 2022);

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

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

- the evaluation table (26 August 2024);
- 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 (The Netherlands, 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 FOR REPRESENTATIVE USES

Bixlozone is an ISO common name for 2-(2,4-dichlorobenzyl)-4,4-dimethylisoxazolidin-3-one (IUPAC).

The formulation for representative uses for the evaluation was 'F9600-4SC', a suspension concentrate (SC) containing 400 g/L of pure bixlozone.

The representative uses evaluated were broadcast soil spray application for control of annual grasses and broad-leaved weeds in pre-emergence crops of winter cereals (wheat and barley), winter oilseed rape and maize and in early post-emergence crops of winter wheat in Central and Southern EU zone. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix B.

The information on the active substance, the formulation for representative uses, including the co-formulants in this formulation, was considered in the overall assessments during the peer review. None of the co-formulants is an unacceptable co-formulant listed in Annex III of Regulation (EC) No 1107/2009,[3] and one component of a co-formulant is a currently not approved active substance under Regulation (EC) No 1107/2009. Details on the composition of the formulations cannot be reported in conclusions because of the provisions in Article 63(2)(d) of Regulation (EC) No 1107/2009, however this information was fully available and evaluated during the peer review. A proposal for classification of the formulation according to the Regulation (EC) 1272/2008 was provided by the applicant and assessed by the RMS (please see Volumes 3 CP of the DAR).

Data were submitted to conclude that the uses of bixlozone according to the representative uses proposed at EU level result in a sufficient herbicidal efficacy against the target weeds, following the guidance document SANCO/10054/2013 – rev. 3 (European Commission, 2013).

CONCLUSIONS OF THE EVALUATION

General aspects

With regard to the mammalian toxicity information available for the formulation for representative uses F9600-4SC, studies were performed for acute toxicity and genotoxicity endpoints. With regard to the co-formulants contained in F9600-4SC, sufficient toxicological data were available for all components, but five. For two components of a co-formulant, present at concentrations well below 10% in the final formulation, the experts considered that the available toxicological information did not sufficiently address the genotoxicity. For two components of another co-formulant and for another co-formulant, both present in significant amounts, the experts considered that the available toxicological information did not sufficiently address the genotoxicity and repeated dose toxicity potential of 'F9600-4SC' over 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).[4]

The availability of ecotoxicity data with the formulation for representative uses was discussed at the experts' meeting[5] (refer to Section 5). Furthermore, the experts also discussed the data retrieval search and the available data for the individual components. Considering the reasoning agreed by the experts, no concerns were identified. This conclusion was considered provisional pending more detailed data retrieval done by the applicant.

[3]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.

[4]See experts' consultation point 2.7 at the Pesticide Peer Review Teleconference 125–129 (January – February 2024) (EFSA, 2024).

[5]See experts' consultation point 0.3 at the Pesticide Peer Review Teleconference 125–129 (January – February 2024) (EFSA, 2024).

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).

The proposed specification for bixlozone is based on batch data from pilot plant productions. The proposed minimum purity of the technical material is 960 g/kg. *N*,*N*,*N*-tributylbutan-1-aminium bromide (TBAB) was considered as a relevant impurity with maximum content of 2 g/kg (see Section 2). It should be noted that evaluation of the toxicological relevance of an impurity is not concluded (see Section 2), as a consequence, new data such as spectral data, content of the impurity before and after the storage of the formulation and method for analysis of the relevant impurity in the formulation might be required. It cannot be concluded if the batches used in toxicological studies were fully representative of the proposed reference specification (see Section 2). The batches used in the ecotoxicological assessment support the proposed specification (See Section 5). It should be noted that according to Regulation (EU) No 283/2013 information on the analytical profile of batches should again be provided once industrial scale production methods and procedures have been stabilised. There is no FAO specification available for bixlozone.

The main data regarding the identity of bixlozone and its physical and chemical properties are given in Appendix B. TBAB was concluded as a relevant impurity thus its spectral data, its content before and after the storage of the formulation and a method for analysis in the formulation is required (**data gap**, see Section 10).

Adequate methods are available for the generation of data required for the risk assessment. The extraction efficiency of the method used in support of residue studies was not properly addressed[6] (**data gap**, see Section 10). Methods of analysis are available for the determination of the active substance in the technical material and in the representative formulation and for the determination of the respective impurities in the technical material.

Bixlozone residues can be monitored in food and feed of plant origin by using liquid chromatography with tandem mass spectrometry (LC–MS/MS) with limit of quantification (LOQ) of 0.01 mg/kg in each commodity group. The extraction efficiency of the method in dry, high water, high oil and high-acid content commodities was not addressed, yet a data gap was set only for high-water commodities (**data gap**, see Section 10) as, according to the representative uses, residues above the LOQ were found only in these commodities (see Section 3).

5-hydroxy-bixlozone residues in animal products can be determined by QuEChERS using LC–MS/MS with LOQ of 0.01 mg/kg in all animal matrices. LC–MS/MS method including a hydrolysis step is available for determination of 5-hydroxy-bixlozone conjugates, with a LOQ 0.005 mg/kg in milk and 0.01 mg/kg in all other animal matrices. However, the efficiency of the hydrolysis step was not fully justified and an ILV of this method was not provided (**data gaps**, see Section 10). The efficiency of the extraction procedures used in both methods was not verified as residues in the animal matrices above LOQ, as a result of the representative uses, are not expected (see Section 3).

Bixlozone residues in soil, water (surface and drinking water) and air can be monitored by LC–MS/MS with LOQs of 0.005 mg/kg, 0.1 µg/L and 0.36 µg/m^3, respectively.

Bixlozone residues in body fluids (blood and urine) can be determined by LC–MS/MS with LOQ of 0.05 mg/L. Bixlozone residues in body tissues can be determined by QuEChERS using LC–MS/MS with LOQ of 0.01 mg/kg.

2 | MAMMALIAN TOXICITY

The toxicological profile of the active substance bixlozone and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting Teleconference (TC) 125 in January 2024. The assessment is based on the following guidance documents: European Commission (2003, 2012a), EFSA (2014c, 2017), EFSA PPR Panel (2012).

Regarding the proposed reference specification (RS), the impurity TBAB is identified as relevant, with maximum acceptable levels at 0.2%. However, for another impurity insufficient information for the assessment of the toxicological relevance has been provided. Accordingly, it could not be concluded if its proposed maximum level is acceptable and if the batches used in the toxicological studies were fully representative of the proposed reference specification (**data gap** leading to an issue not finalised, see Section 9.1).

The **oral absorption** of bixlozone is estimated to account for 70% of the administered low dose.

Excretion occurs predominantly through the urine and to a more limited extent in the faeces following biliary excretion into the gut. In the rat, bixlozone is widely **distributed** throughout the body, with the highest levels being reached in gastrointestinal (GI) tract, carcass, liver and blood, and there is no evidence for bioaccumulation. Bixlozone is almost completely metabolised. The main **metabolic** pathway identified is oxidation (hydroxylation), and heterocyclic ring-opening followed by glucuronidation of the oxidative products. Major rat urinary metabolites are carbamic acid, 2,4-dichlorohippuric acid, 5-keto-hydrate-F9600, F9600-cysteine derivative and 5-Hydroxy-F9600. Most prominent metabolite in faeces is 5-hydroxy-F9600 followed by 3-hydroxypropanamide-F9600.

Based on comparative in vitro metabolism, no major metabolic inter-species (mouse, rat, rabbit, dog) differences have been observed and no metabolites unique to humans have been identified.

[6]See open point 1.9 in the Evaluation table (EFSA, 2024).

The **residue definition** for body fluids and tissues is bixlozone.

Bixlozone has low **acute** toxicity by oral, dermal and inhalation exposure, and has no irritating or sensitising properties. Testing for phototoxicity is not required for this active substance as in accordance with data requirements laid down in Commission Regulation (EU) No 283/2013, since the ultraviolet/visible molar extinction/absorption coefficient of the active substance is less than 10 $L \times mol^{-1} \times cm^{-1}$.

Short-term oral toxicity studies were provided for rats, mice and dogs. In all three species the target organ for bixlozone is the liver showing an increase in absolute and relative weight and hypertrophy. In the rat, also kidney weight was increased. The rat and the dog were the most sensitive species with a no observed adverse effect level (NOAEL) in 90-day studies of 29 and 30 mg/kg body weight (bw) per day, respectively.

Based on the available **genotoxicity** data package, the substance is unlikely to be genotoxic. Testing for photomutagenicity is not required for bixlozone as in accordance with data requirements laid down in Commission Regulation (EU) No 283/2013.

After **long-term exposure**, the target toxicity organs included liver (rat and mouse) and kidney (only rat), plus it was also observed a decreased sperm count (in mouse only). The lowest relevant NOAEL is 32 mg/kg bw per day from the 18-month study in mice, based on liver increased weight (absolute and relative), hypertrophy and necrosis, decreased body weight and decreased food consumption.

The substance showed no treatment-related increased incidence of tumours in rats or mice and it was concluded unlikely to be **carcinogenic** for humans in line with the ECHA Risk Assessment Committee (RAC) Opinion (ECHA RAC, 2023).

With regard to **reproductive toxicity** studies, fertility and overall reproductive performance were not affected at up to 140 mg/kg bw per day, identified as the **reproductive NOAEL**. In the multigeneration rat study, the **parental NOAEL** is 34 mg/kg bw per day based on reduced body weight and body weight gain, increased liver and kidney weights, and increased incidence of mononuclear cell infiltration in the prostate. The **offspring NOAEL** is 59 mg/kg bw per day based on reduced body weight gain.

With regard to **foetal development**, no teratogenic effect was observed in rabbits. In the rabbit teratogenicity study, the maternal NOAEL is 200 mg/kg bw per day based on reduced body weight gain and food consumption, and the developmental NOAEL is ≥ 400 mg/kg bw per day with no adverse effects observed.

In the rat teratogenicity study, the maternal NOAEL is 75 mg/kg bw per day based on reduced body weight gain and food consumption, liver weight increase (both absolute and relative) accompanied by hepatocellular hypertrophy and the developmental NOAEL is 225 mg/kg bw per day based on increased skeletal variations (with coinciding maternal toxicity).

The substance was concluded unlikely to be **neurotoxic** or **immunotoxic** in humans.

Toxicological reference values (TRVs) have been derived for bixlozone.[7] The **acceptable daily intake** (**ADI**) is 0.29 mg/kg bw per day, based on the rat 90-day study as supported by the dog 90-day, the two-generation toxicity study in rat, the rat 2-year-study and the mouse 18-month-study applying a standard uncertainty factor (UF) of 100 to account for inter- and intra-individual variability. The **acute reference dose** (**ARfD**) is 0.75 mg/kg bw based on the maternal NOAEL in the rat prenatal developmental toxicity study using the standard UF of 100. The **acceptable operator exposure level** (**AOEL**) is 0.20 mg/kg bw per day, based on the 90-day rat study as supported by the 90-day dog study and the two-generation study in rats, applying a standard UF of 100 and a correction factor for limited oral absorption of 70%. The **acute AOEL** (**AAOEL**) is 0.53 mg/kg bw per day, based on the maternal NOAEL in the rat prenatal developmental toxicity study applying standard UF of 100, as well as a correction factor for limited oral absorption of 70%.

Dermal absorption of bixlozone in the representative product F9600-4SC has been assessed in an in vitro study with human skin. Based on the EFSA guidance (EFSA PPR Panel, 2012), the dermal absorption values to be used for risk assessment are 0.4% for the concentrate (364 g/L), 6% for the 3.36 g/L spray dilution and 24% for the 0.251 g/L spray dilution. Dermal absorption values according to the EFSA guidance of 2017 (EFSA, 2017) are also reported for completeness, i.e. 0.66% for the concentrate (364 g/L), and 11% and 31% for the 3.36 g/L and 0.251 g/L spray dilutions, respectively, since they might be further considered at MS level for national authorisations.

The **non-dietary exposure** estimates for the operators are below the (A)AOEL without the use of gloves during mixing/loading and application (using standard workwear), when considering the highest application rate for F9600-4SC of 0.375 kg a.s./ha based on the EFSA calculator (2014c). For the workers, the use of workwear is sufficiently protective during crop inspection according to the EFSA calculator, with exposure estimates below the (A)AOEL; for residents and bystanders, exposure estimates are well below the (A)AOEL and do not require mitigation measures.

Metabolites of bixlozone found in groundwater and/or in animals/plants were discussed at peer review experts' meetings TC 125.[8] As regards metabolites dimethylmalonic acid (free and conjugated), 2,2-dimethyl-3-OH-propionic acid (free and conjugated), F9600-dimethyl-malonamide, F9600-hydroxy-isobutyramide and F9600-3-OH-Propanamide, no conclusions can be drawn on their genotoxicity and general toxicity since no experimental data and only an inconclusive QSAR analysis were submitted for their hazard identification (**data gap**, see also Sections 3 and 9.1.1). The same TRVs of the parent bixlozone are considered applicable to the residue metabolite 5-hydroxy-F9600 which is also a major rat metabolite (see Section 3). The residue and groundwater metabolite 2,4-dichlorobenzoic acid (2,4-DCBA) (free and conjugated) is unlikely to be genotoxic. Since it is considered as a major rat metabolite (when considering its glycine conjugate, 2,4-dichlorohippuric acid), the reference values of bixlozone may also cover 2,4-DCBA (see Sections 4 and 7).

[7] See Experts' Consultation 2.5 of the Pesticides Peer Review Experts' Meeting TC 125 (EFSA, 2024).

[8] See Experts' Consultation 2.4 of the Pesticides Peer Review Experts' Meeting TC 125 (EFSA, 2024).

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).

Bixlozone was discussed at the Pesticides Peer Review Experts' meeting 128 in January 2024.

Metabolism of bixlozone in primary crops was investigated in oilseed rape, sugar beet, wheat and rice with soil application at crop emergence. Bixlozone was not recovered in any of the investigated crops and several metabolites were identified; 2,2-dimethyl-3-OH-propionic acid (M118/1) and 2,4-dichlorobenzoic acid (M190/1) were found in all crops up to 44% and 68% TRR, respectively. F9600-dimethyl-malonamide (M289/2) was identified in rice straw (13% TRR), sugar beet tuber and leaves (30% and 55% TRR). Metabolite dimethylmalonic acid (M132/1) was found in sugar beet tuber (34% TRR), rice grain (20% TRR) and rice straw (15% TRR). 5′-Hydroxy-F9600 (M289/3) was major in wheat straw (48% TRR).

Field trials analysing for bixlozone, 2,2-dimethyl-3-OH-propionic acid, 2,4-dichlorobenzoic acid and 5′-Hydroxy-F9600 in cereals (wheat, barley, maize) and oilseed rape were available. The GAP deviation in terms of a less critical BBCH in oilseed rape trials was deemed acceptable, as it is not expected to affect residue levels. For metabolites 2,2-dimethyl-3-OH-propionic acid (found in maize (cereal) grain up to 0.3 mg/kg) and its downstream metabolite dimethylmalonic acid, the claim that their complete presence is due to natural occurrence and not as a residue of bixlozone was not sufficiently demonstrated (**data gap**, see Section 9.1.1). Thus, the inclusion of 2,2-dimethyl-3-OH-propionic acid and dimethylmalonic acid in the plant risk assessment residue definition (RA-RD) and data on their toxicological profile might be needed upon submission of the requested information. Metabolite 2,4-dichlorobenzoic acid, was not found above 0.01 mg/kg in food items and above 0.05 mg/kg in feed items in none of the trials. Metabolite 5′-Hydroxy-F9600 was found in overdosed field trials in wheat and barley straw up to 0.02 mg/kg, suggesting its presence at potentially more critical future GAPs. Calculated livestock dietary burden for 5′-Hydroxy-F9600 was not exceeded for the representative uses.

Given the occurrence of F9600-dimethyl-malonamide in rice and sugar beet metabolism studies and in absence of field trials data in root and tuber crops, investigation of F9600-dimethyl-malonamide and its toxicological profile should be considered for future uses in primary crops belonging to root and tuber, rice and leafy crops.

Residue definition for enforcement for all crops treated pre- and post-emergence is proposed as 'bixlozone' by default.

The provisional risk assessment residue definition is 'bixlozone, free and conjugated' for all crops for pre- and post-emergence, pending the requested data on natural occurrence of 2,2-dimethyl-3-OH-propionic acid and dimethylmalonic acid (see data gap above). Considering the presence of the metabolite 5′-Hydroxy-F9600 in feed items in the available metabolism studies as well as in the overdosed field trials, its presence at potentially more critical future GAPs may be expected. On this basis, a provisional **risk assessment residue definition only for cereal feed items (forage, hay and straw)** is 'bixlozone, free and conjugated and 5′-Hydroxy-F9600, free and conjugated'. The expression of this residue definition will depend on the toxicological profile of the metabolite 5′-Hydroxy-F9600 once it becomes needed (i.e. once more critical GAPs result in higher residues, leading to exceedance of animal dietary burden trigger values).

A study investigating bixlozone metabolism in rotational crops, showed similar qualitative metabolic pattern as in primary crops except for root and tuber where bixlozone compound was found at 75% TRR (radish roots). Major metabolites were dimethylmalonic acid (M132/1) in lettuce, radish roots, radish tops and wheat straw, (up to 47% TRR), 2,4-dichlorobenzoic acid in wheat grain, radish roots and tops (up to 30% TRR), F9600-hydroxy-isobutyramide (M261/1) in radish tops (up to 37% TRR), 5′-Hydroxy-F9600 in wheat feed items (up to 41% TRR) and F9600-dimethyl-malonamide in lettuce and radish roots (up to 30% TRR).

Three rotational crops field trials instead of four, dosed at 0.8N rate that covers bixlozone soil accumulation, and analysing bixlozone and metabolites 5′-Hydroxy-F9600, 2,4-dichlorobenzoic acid.

F9600-dimethyl-malonamide, F9600-hydroxy-isobutyramide, dimethylmalonic acid were available (**data gap,** Section 10). Bixlozone and F9600-dimethyl-malonamide were found in spinach leaves at 0.02 mg/kg and in radish leaves at 0.1 and 0.02 mg/kg respectively. Metabolite F9600-hydroxy-isobutyramide was also found in radish leaves above LOQ in one sample only. Dimethylmalonic acid was detected in spinach (0.03 mg/kg) and additional evidence demonstrating that it occurs also naturally, as claimed by the applicant, is requested (**data gap**, see Section 9.1.1). All the remaining investigated metabolites were not found at relevant amounts in food and feed. In order to extrapolate the data and to derive an MRL for the whole group of leafy vegetables and brassicas, additional field trials are needed (**data gap**, see Section 9.1.1).

Risk assessment residue definition for rotated crops (only leafy crops) is 'Bixlozone, free and conjugated and F9600-dimethyl-malonamide, free and conjugated'. The risk assessment residue definition is provisional, and the expression is pending the information on the toxicity of F9600-dimethyl-malonamide.

Risk assessment residue definition for rotated crops (except leafy crop) is 'Bixlozone free and conjugated'. The risk assessment residue definitions are provisional due to further data requested on natural occurrence of dimethylmalonic acid metabolite and toxicological data requested for F9600-hydroxy-isobutyramide.

Storage stability was demonstrated for all the compounds investigated in the residue field trials, except for dimethylmalonic acid. This data might be requested pending the finalisation of the risk assessment residue definition.

Metabolism studies in hen and goat showed a complete bixlozone degradation into several metabolites. Major metabolites identified in goat and hen matrices were 5-Hydroxy-F9600 (M289/1) (80% TRR milk, 31% TRR eggs) and F9600-dimethyl-malonamide (up to 27% TRR muscle). F9600-3-OH-propanamide (M275/1) was found in goat study (30% TRR) and dimethylmalonic acid was found in hen matrices (58% TRR). Since these metabolites were found at relevant levels in the

livestock metabolism studies and considering that residues in animal food commodities > 0.01 mg/kg cannot be excluded, further data is needed to address the relevance of dimethylmalonic acid, F9600-dimethyl-malonamide and F9600-3-OH-propanamide for the consumer dietary risk assessment (**data gap**, see Section 9.1.1). For the time being a **provisional risk assessment residue definition for animals** is derived as '5-Hydroxy-F9600, free and conjugated expressed as bixlozone', pending the data gap identified for the rest of the metabolites.

As the feed metabolite 5'-Hydroxy-F9600 was not found in animal matrices, its fate in animals might be reconsidered in case future uses would trigger animal dietary burden.

Residue definition for enforcement for all animal matrices is '5-Hydroxy-F9600, free and conjugated, expressed as bixlozone' according to the 'best marker' concept. In view of the assessment of a new active substance, maximum residue levels for animal commodities are proposed at the LOQ of the proposed monitoring method (see Section 1).

Under standard hydrolysis conditions bixlozone remains stable. F9600-dimethyl-malonamide, relevant for food items available from rotated crops, should be further investigated under the standard hydrolysis conditions (**data gap**, see Section 9.1.1). In addition, pending the finalisation of the plant and animal risk assessment residue definitions, other metabolites also may need to be investigated.

As regards the residues in pollen and bee products for human consumption, eight field trials in oilseed rape flowers were available. They were analysed for bixlozone (found at max. 0.05 mg/kg), 2,2-dimethyl-3-OH-propionic acid (found at 0.06 mg/kg), 2,4-dichlorobenzoic acid and 5'-Hydroxy-F9600 (both not detected). Based on these findings an MRL of 0.05 mg/kg could be proposed. The relevance of the metabolite 2,2-dimethyl-3-OH-propionic acid in bees products is pending the confirmation on its natural occurrence in plants.

Studies addressing bixlozone metabolism in fish were not submitted and the need for them is pending the finalisation of the risk assessment residue definition in plants.

Chronic and acute consumer dietary intakes were performed for residue from plant commodities and the derived toxicological reference values, using the revision 3.1 of the EFSA PRIMo (Pesticide Residue Intake Model). The calculated theoretical maximum daily intake (TMDI) accounts for 0.2% of the ADI. The international estimated short-term intake (IESTI) reaches a maximum of 0.4% of the ARfD (UK infant, potatoes). This risk assessment was only performed for bixlozone and does not consider any of the metabolites nor all relevant rotational crops. This because it is pending the confirmation of residue levels of metabolites and data on toxicity are missing, and accordingly the residue definition for risk assessment for plants and animals cannot be finalised. Therefore, the calculations are provisional, pending the fulfilment of the pertinent data gaps (see Section 9.1.1).

The consumer risk assessment from the consumption of drinking water is also not finalised considering the lack of appropriate information to address the effect of water treatment processes (via chlorination) on the nature of residues of the active substance and its identified metabolites, that might be present in surface water or groundwater, when surface water and/or groundwater are abstracted for the production of drinking water (see Sections 4 and 9.1.1).

The consumer exposure estimates for the groundwater metabolite 2,4-dichlorobenzoic acid were based on the default assumptions laid down in the WHO Guidelines (WHO, 2011) for drinking water quality for (a) a 60-kg adult drinking 2 L of water per day, (b) a 10-kg child drinking 1 L of water per day and (c) a 5-kg bottle-fed infant drinking 0.75 L of water per day. The highest exposure accounted for 0.15% of the ADI (infant).

4 | ENVIRONMENTAL FATE AND BEHAVIOUR

Bixlozone was discussed at the Pesticides Peer Review Meeting Teleconference (TC) 127 in January 2024.

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, bixlozone exhibited moderate to high persistence. No major metabolites (> 10% applied radioactivity (AR)) were formed. Mineralisation of the phenyl-U-^{14}C and carbonyl-^{14}C radiolabels to carbon dioxide accounted for 10%–47% AR and 12%–54% AR after 120 days, respectively. The formation of unextractable residues (not extracted by acetonitrile, acetonitrile/water and acetonitrile/water/formic acid) for these radiolabels accounted for 3.8%–18.2% AR and 3.3%–11.6% AR after 120 days, respectively. In anaerobic soil incubations, bixlozone degraded more slowly than under aerobic conditions, forming the degradation product **2,4-dichlorobenzoic acid** (max 5.8% AR and increasing, at the end of the study) which triggered further exposure assessment for the representative use on winter cereals and oilseed rape. Under aerobic conditions, the metabolite F9600-3-OH-propanamide (formed in the aquatic system at levels triggering an aquatic risk assessment) exhibited very low persistence in soil and metabolite 2,4-dichlorobenzoic acid exhibited low persistence in soil. Under soil photolysis conditions, the degradation of bixlozone was observed to be higher when exposed to light compared when it was not, although the overall degradation rates remained slow. Bixlozone exhibited medium to low mobility in soil. Metabolite F9600-3-OH-propanamide exhibited high-soil mobility and metabolite 2,4-dichlorobenzoic acid exhibited very high-soil mobility. It was concluded that the adsorption of bixlozone and metabolite F9600-3-OH-propanamide was not pH dependent. The experts of the TC 127 agreed that 2,4-dichloro benzoic acid is expected to exhibit pH dependent adsorption, but that a significant adsorption should only be expected at low pH values in soil. Considering the available adsorption endpoints, the experts agreed that a geometric mean K_{Foc} value and an arithmetic mean 1/*n* value of the three soils above pH 7 should be used for the groundwater exposure assessment.

In satisfactory field dissipation studies carried out at six sites from Germany, UK, Italy and France using the F9600-4 SC (the formulation for representative uses) and/or F9600-21 CS formulations, bixlozone exhibited moderate to high persistence. In all locations, the formulations were applied to bare soil, and in some instances, they were incorporated into the top few centimetres of soil immediately after application. Metabolite F9600-3-OH-propanamide levels were below the detectable limit, while the percentage of 2,4-dichlorobenzoic acid relative to the initial bixlozone amount ranged from 0.7% to 34.7% just after the application. Consequently, this metabolite was included in soil and groundwater exposure assessments. Only the results from the field trials where the SC formulation was applied and incorporated directly after application were considered relevant for modelling purposes by the experts of the TC 127.[9] Field DT50 values were accepted as being reasonable estimates of degradation and were normalised to FOCUS reference conditions (20°C and pF2 soil moisture) using the time step normalisation procedure in accordance with FOCUS (2006) kinetics guidance. The field data endpoints were not combined with laboratory values to derive modelling endpoints for bixlozone. Although they are not used in the current evaluation, reliable field degradation/dissipation endpoints derived from trials conducted with CS formulation are presented in Appendix B as they may be useful if an assessment of representative uses with this type of formulation is required at the national level.

In laboratory incubations in dark aerobic natural water-sediment systems, bixlozone exhibited moderate persistence, forming the major metabolites 2,4-dichlorobenzoic acid (max. 30.4% AR in water and max. 10.5% AR in sediment), **F9600-3-OH-propanamide** (max 7.6% AR in sediment), **F9600-dimethyl-malonamide** (max. 10.6% AR in water) and **4-carboxy-F9600** (max. 15.0% AR in water). The unextractable sediment fraction (not extracted by acetonitrile/water) was a limited sink for the phenyl-U-^{14}C and carbonyl-^{14}C radiolabels, accounting for 8%–14% AR and 8%–12% AR, respectively, at study end (100 days). Mineralisation of these radiolabels accounted for 7%–9% AR and 30%–52% AR, respectively, at the end of the study. The rate of decline of bixlozone in a laboratory sterile aqueous photolysis experiment was slow relative to that occurred in the aerobic water-sediment incubations. No chromatographically resolved component (excluding bixlozone) accounted for > 5% AR. The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites 2,4-dichlorobenzoic acid, F9600-3-OH-propanamide, F9600-dimethyl-malonamide and 4-carboxy-F9600 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 bixlozone, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[10] The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 58%–86% spray drift reduction) and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion run-off of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. Due to the vapour pressure of bixlozone being > 10^{-4} Pa (at 20°C), FOCUS Step 4 PECsw/PECsed calculations for bixlozone also considered the contribution of the short-range transport and the subsequent off-target depositions onto water bodies. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that whilst run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2000 mL/g (i.e. bixlozone), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature than for more strongly adsorbed compounds.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4.[11] The potential for groundwater exposure from the representative uses by bixlozone above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all 9 FOCUS groundwater scenarios.

For metabolite 2,4-dichlorobenzoic acid the 80th percentile annual average recharge concentrations leaving the 1 m soil layer were estimated to be > 0.1 µg/L in all or more than half of the pertinent FOCUS groundwater scenarios. In particular:

- For the representative uses on winter cereals (BBCH 00–09), the 80th percentile annual average recharge concentrations leaving the 1 m soil layer were estimated to be > 0.1 µg/L at seven out of nine FOCUS scenarios (PECgw range 0.13–2.88 µg/L).
- For the representative uses on winter cereals (BBCH 11–13), the 80th percentile annual average recharge concentrations leaving the 1 m soil layer were estimated to be > 0.1 µg/L at seven out of nine FOCUS scenarios (PECgw range 0.12–2.88 µg/L).
- For the representative uses on winter oilseed rape, concentrations expressed on this basis were estimated to be > 0.1 µg/L at all six pertinent scenarios (PECgw range 0.23–2.26 µg/L).
- For the representative uses on maize, concentrations expressed on this basis were estimated to be > 0.1 µg/L at seven out of eight scenarios (PECgw range 0.13–2.27 µg/L).

Based on the information available in the mammalian toxicity section, this metabolite is considered to be non-relevant for human health (see Sections 2 and 7).

[9]See Experts' Consultations 4.1 and 4.5 of the Pesticides Peer Review Experts' Meeting TC 127 (EFSA, 2024).

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

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

The applicant provided appropriate information to address the effect of water treatments processes via ozonation on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for the production of drinking water. However, this information was inadequate to address the effect of the chlorination process on the nature of the residues that might be present in surface water or groundwater when surface water and/or groundwater are abstracted for the production of drinking water.[12] This has led to the identification of a data gap and results in the consumer risk assessment not being finalised (see Sections 3 and 9.1.1).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in the 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.

5 | ECOTOXICOLOGY

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

Bixlozone was discussed at the Pesticides Peer Review Experts' Meeting Teleconference 129 in January–February 2024.

The information to support the compliance of the batches used in the ecotoxicological studies with the proposed reference specification was considered sufficient.

Acute and reproductive studies with bixlozone were available for **birds** and **wild mammals**. In addition, an acute study with the formulation for the representative uses, F9600-4SC, was available. A low acute and reproductive risk was concluded at the screening step for birds and wild mammals for all representative uses.

Several valid studies with bixlozone and F9600-4SC covering the relevant **aquatic taxa** (i.e., fish, aquatic invertebrates, algae, aquatic macrophytes and sediment-dwelling organisms) were available. The experts discussed the validity of some aquatic studies.[13] The experts discussed and agreed upon several refinements for aquatic invertebrates ('species sensitivity distribution' approach based on acute data from eight species) and macrophytes ('geometric mean' approach using data from four species). Low risk to fish and algae was indicated at $FOCUS_{sw}$ Step 1 for all representative uses while low risk to aquatic invertebrates was indicated at $FOCUS_{sw}$ Step 3 for the uses in winter barley and wheat (acute risk) and the uses in maize (acute and chronic risk). High risk to aquatic invertebrates was indicated at $FOCUS_{sw}$ Step 4 for the representative uses in winter barley and wheat (chronic risk for 1/9 scenarios) and winter oilseed rape (acute and chronic risk for 1/6 scenarios). Also, high risk to macrophytes was indicated at $FOCUS_{sw}$ Step 4 for the representative uses in winter barley and wheat (3/9 scenarios) and winter oilseed rape (1/6 scenarios). Low risk to all aquatic organisms was concluded for the uses on maize at $FOCUS_{sw}$ Step 4 when considering risk mitigation measures consisting of 20 m no-spray buffer zone in combination with a 20 m vegetated filter strip. Toxicity data on the most sensitive taxa were available for the pertinent metabolites 2,4-dichlorobenzoic acid, 4-carboxyl F9600, F9600-dimethyl-malonamide, F9600-3-OH-propanamide. For all metabolites, low risk could be concluded for all aquatic taxa and for all the representative uses.

Acute (oral and contact) and chronic (adult) toxicity studies with honey **bees** were available with bixlozone and the formulation for representative uses while chronic (adult and larvae) studies were available with bixlozone. In addition, an adult chronic study with a formulation (F9600-47) different than the one for the representative uses was submitted. The ecotoxicological equivalence of both formulations could not be determined and, therefore, the chronic study was not used in the risk assessment. The risk assessment performed in line with the SANCO guidance on terrestrial ecotoxicology (European Commission, 2002) indicated a low acute risk to honey bees from contact and oral exposure for all representative uses. The same conclusion was reached by applying the EFSA bee guidance document (EFSA, 2013) at the screening step. A low chronic risk to larvae was concluded at tier-1 (all uses) whereas low chronic risk to adults honey bee for the scenario 'weeds present in the treated field' could not be concluded at tier-1 for any of the representative uses. It should be noted, however, that new scientific knowledge (EFSA, 2023) indicates that the weed scenario is not relevant for winter cereals at BBCH ≤ 20. A suitable assessment of accumulative and sublethal effects was not available (**data gap** for sublethal effects, see Section 10). Acute (oral and contact) studies with bixlozone were available with the bumblebee *Bombus terrestris* and the solitary bee *Osmia bicornis*. Low acute risk was indicated at the screening step for all representative uses.

For **non-target arthropods other than bees**, tier 1 (glass plate) studies with the standard species *Aphidius rhopalosiphi* and *Typhlodromus pyri* as well as extended laboratory studies with *T. pyri* and *Chrysoperla carnea* were available with the formulation for representative uses (F9600-4SC). A low in- and off-field risk was concluded for the representative uses of bixlozone.

The risk to **earthworms** (*Eisenia fetida*) and other **soil macroorganisms** (i.e. the Collembola *Folsomia candida* and the predatory mite *Hypoaspis aculeifer*) was evaluated using chronic toxicity studies with the active substance and/or the formulation for representative uses. Based on the available data and the risk assessment, a low long-term risk was concluded for all the representative uses of bixlozone. Toxicity data with the metabolite 2,4-dichlorobenzoic acid was only available for earthworms. For the other soil macroorganisms, the risk assessment was performed assuming the metabolite to be 10

[12]See Column E of the Evaluation Table section 4, under Data Requirement 4.4 (EFSA, 2024).

[13]See experts' consultation points 5.1 and 5.2 at the Pesticides Peer Review Experts' Meeting Teleconference 129 (January–February 2024) (EFSA, 2024).

times more toxic than the parent compound. Low risk was concluded for bixlozone and 2,4-dichlorobenzoic for all representative uses.

Nitrogen transformation studies with the formulation for representative uses and 2,4-dichlorobenzoic acid were available to address the risk to **soil microorganisms**. A low risk was indicated for all representative uses.

Several aspects related to the hazard and risk assessment to **non-target terrestrial plants** were discussed at the experts' meeting.[14] The experts agreed that, although the vegetative vigour and the seedling emergence studies available with the formulation for representative uses presented several limitations, both could be used to address the risk from exposure to bixlozone. Based on the available data and the risk assessment using the standard endpoints, low risk to all representative uses could be concluded upon applying risk mitigation measures (see Table 6).

A low risk to organisms involved in biological methods for **sewage treatment** could be concluded for all representative uses.

6 | ENDOCRINE DISRUPTION PROPERTIES

The endocrine disruption properties of bixlozone were discussed at the Pesticides Peer Review Joint Mammalian Toxicology-Ecotoxicology Experts' Teleconference (TC) 124 (22nd–30th January 2024).

With regard to the assessment of the endocrine disruption potential of bixlozone for **humans,** according to the ECHA/EFSA ED Guidance (2018), in determining whether bixlozone 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 bixlozone with the EAS- and T-signalling pathways using the available evidence in the data set.

For the **T modality**, T parameters were considered sufficiently investigated and a pattern of T-mediated adversity was not identified. Therefore, based on the available and sufficient dataset, it was concluded that the ED criteria are not met for the T modality (**Scenario 1a** of the ECHA/EFSA (2018) ED Guidance).

Regarding the **EAS-modalities**, EAS parameters were considered sufficiently investigated and a pattern of EAS-mediated adversity was not identified. Therefore, based on the available and sufficient dataset, it was concluded that the ED criteria are not met for the EAS modalities (**Scenario 1a** of the ECHA/EFSA (2018) ED Guidance).

The outcome of the assessment reported above for humans also applies to **wild mammals as non-target organisms**, as also discussed at the experts' meeting.[15]

For **non-target organisms other than mammals**, a Fish Short-Term Reproductive Assay (OECD TG 229) and an amphibian metamorphosis assay (OECD TG 231) were available to sufficiently investigate the endocrine activity of Bixlozone through the EAS- and T-modalities, respectively. The findings from the available studies, the WoE and its related uncertainty analysis[16] were further discussed at the Pesticides Peer Review Experts' Meeting TC 124[15].

The available AMA was considered valid. Overall, based on the effects observed[15], the AMA did not show any pattern of T-mediated endocrine activity.

The available FSTRA was considered as reliable with restrictions based on the observed limitations i.e. setting of the testing concentrations based on effects observed on fecundity (sensitive parameter for EAS) and excess of food in two range-finding tests, VTG results considered not reliable due to the high variability and insufficient methodological information. Overall, when considering the results from the FSTRA[15], the WoE from all the available information and the related uncertainties[16] it can be concluded that it is unlikely that bixlozone may elicit related adverse effects through interference with the hypothalamus–pituitary–gonad (HPG axis).

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 bixlozone 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 1–5)

TABLE 1 Soil.

Compound (name and/or code)	Ecotoxicology
Bixlozone	Low risk to soil organisms
2,4-dichlorobenzoic acid	Low risk to soil organisms

[14]See experts' consultation point 5.3 at the Pesticides Peer Review Experts' Meeting Teleconference 129 (January–February 2024) (EFSA, 2024).

[15]See experts' consultation 5.4 of the Pesticides Peer Review Experts' Meeting Report TC 124 (EFSA, 2024).

[16]Please refer to the uncertainty analysis table in vol 3 CA B9 of the DAR (The Netherlands, 2024).

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
Bixlozone	No				
2,4-dichlorobenzoic acid	Yes Winter cereals: 7/9 scenarios (0.12–2.88 μg/L) Winter oilseed rape: 6/6 scenarios (0.23–2.26 μg/L) Maize: 7/8 scenarios (0.13–2.27 μg/L)	No	No Unlikely to be genotoxic Covered by the parent's TRVs	Yes	Not triggered

[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 (2014) guidance.

TABLE 3 Surface water and sediment.

Compound (name and/or code)	Ecotoxicology
Bixlozone	Low risk for the uses in maize considering risk mitigation measures High risk for the uses in winter barley and wheat and winter oilseed rape
2,4-dichlorobenzoic acid	Low risk to aquatic organisms
4-carboxyl-F9600	Low risk to aquatic organisms
F9600 dimethyl-malonamide	Low risk to aquatic organisms
F9600-3-OH-propanamide	Low risk to aquatic organisms

TABLE 4 Air

Compound (name and/or code)	Toxicology
Bixlozone	LC_{50} > 2.11 mg/L air/4 h (nose only; target dose of 2.11 mg/L)

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. 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.

8.1 | Particular conditions proposed for the representative uses evaluated

TABLE 5 Risk mitigation measures (RMM) proposed for the representative uses under assessment.

	Winter wheat BBCH 00–09	Winter barley BBCH 10–13	Winter oilseed rape	Maize
Representative use	**Broadcast soil spray application**			
Operator risk	–	–	–	–
Worker exposure	–	–	–	
Bystander/resident exposure				

(Continues)

TABLE 5 (Continued)

	Winter wheat BBCH 00–09	Winter barley BBCH 10–13	Winter oilseed rape	Maize
Representative use	**Broadcast soil spray application**			
Risk to aquatic organisms				RMM equivalent to 20 m no-spray buffer zone combined with a 20 m vegetated filter strip[a]
Risk to non-target terrestrial plants	RMM equivalent to 5 m no-spray buffer zone or 50% drift reducing nozzles	RMM equivalent to 5 m no-spray buffer zone or 50% drift reducing nozzles	RMM equivalent to 5 m no-spray buffer zone or 50% drift reducing nozzles	RMM equivalent to 5 m no-spray buffer zone or 75% drift reducing nozzles

[a]R4/Stream.

9 | CONCERNS AND RELATED DATA GAPS

9.1 | Concerns and related data gaps for the representative uses evaluated

9.1.1 | 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[17] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

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

1. The acceptability of the proposed maximum level of one impurity and the representativeness of the batches used in the toxicological assessment with regard to the proposed reference specification could not be finalised (see Section 1 and 2).

    a. The toxicological relevance of one impurity (addressing QSAR genotoxicity structural alerts) included in the proposed reference specification should be concluded (relevant for all representative uses evaluated; see Section 2).

2. The consumer risk assessment is not finalised pending finalisation of the risk assessment residue definitions for plants and animals due to the following data gaps:

    a. whether and to what extent metabolites 2,2-dimethyl-3-OH-propionic acid and dimethylmalonic acid occur also naturally;
    b. in order to extrapolate the data and to derive an MRL for the whole crop group of leafy vegetables and brassicas, relevant for rotational crops, additional rotational crop field trials, in accordance with the currently applicable guidance, are needed to establish the concentration of residues in this crop group for the consumer risk assessment;
    c. further assessment of the genotoxicity and general toxicity of the residue metabolites dimethylmalonic acid (free and conjugated), 2,2-dimethyl-3-OH-propionic acid (free and conjugated), F9600-dimethyl-malonamide, F9600-hydroxy-isobutyramide and F9600-3-OH-propanamide (relevant for all uses; see Sections 2 and 3);
    d. further data and information to assess the relevance of the livestock metabolites dimethylmalonic acid, F9600-dimethyl-malonamide and F9600-3-OH-propanamide for the consumer dietary risk.
    e. Investigation of F9600-dimethyl-malonamide, relevant for food items available from rotated crops, under the standard hydrolysis conditions.

3. The consumer risk assessment from the consumption of drinking water is not finalised with regard to the unknown nature of residues that might be present in drinking water consequent to water treatment processes (via chlorination), following abstraction of surface water or groundwater that might contain residues of the active substance and its

[17]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.

metabolites 2,4-dichlorobenzoic acid, 4-carboxyl F9600, F9600-dimethyl-malonamide and F9600-3-OH-propanamide (see Sections 3 and 4).

a. Further data and information were not available to demonstrate that residues of bixlozone and its metabolites 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).

9.1.2 | 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:

No critical areas of concern identified.

9.1.3 | Overview of the concerns identified for each representative use considered (Table 6)

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

		Winter wheat				
		BBCH 00–09	BBCH 10–13	Winter barley	Winter oilseed rape	Maize
Representative use		**Soil broadcast spray application**				
Operator risk	Risk identified					
	Assessment not finalised					
Worker risk	Risk identified					
	Assessment not finalised					
Resident/bystander risk	Risk identified					
	Assessment not finalised					
Consumer risk	Risk identified					
	Assessment not finalised	X[2]	X[2]	X[2]	X[2]	X[2]
Risk to wild non-target terrestrial vertebrates	Risk identified					
	Assessment not finalised					
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[a]	X[a]	X[a]	X[b]	X[b]
	Assessment not finalised					
Risk to aquatic organisms	Risk identified	3/9 scenarios	3/9 scenarios	3/9 scenarios	1/6 scenarios	
	Assessment not finalised					
Groundwater exposure to active substance	Legal parametric value breached					
	Assessment not finalised					

(Continues)

TABLE 6 (Continued)

Representative use		Winter wheat BBCH 00–09	Winter wheat BBCH 10–13	Winter barley	Winter oilseed rape	Maize
		Soil broadcast spray application				
Groundwater exposure to metabolites	Legal parametric value breached					
	Parametric value of 10 µg/L[c] breached					
	Assessment not finalised					

Notes: The superscript numbers relate to the numbered points indicated in Sections 9.1.1. Where there is no superscript number, see Sections 2–7 for further information.

[a]Low chronic risk to adults honey bee for the scenario 'weeds present in the treated field' could not be concluded at tier 1 with the EFSA (2013) Guidance Document. It should be noted, however, that new scientific knowledge (EFSA, 2023) indicates that the weed scenario is not relevant for winter cereals at BBCH ≤ 20.

[b]Low chronic risk to adult honey bees ('weeds in the treated field' scenario) could not be concluded at tier 1 with the EFSA (2013) Guidance Document.

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

10 | LIST OF OTHER OUTSTANDING ISSUES

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

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

- For two components of a co-formulant of the formulation F9600-4SC for representative uses, genotoxicity information was not available. For two components of another co-formulant and for another co-formulant, genotoxicity and repeated dose toxicity information over the short- and long-term were not available; therefore, in order to allow a final conclusion on the safety assessment of F9600-4SC, e.g. genotoxicity and repeated dose toxicity data for these components 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').
- Spectral data, information on the content of the relevant impurity TBAB in the formulation before and after the storage of the formulation and a method for its determination in the formulation (relevant for all representative uses evaluated; see Section 1).
- Assessment of the extraction efficiency of the method used in support of the residue studies (plants) for all metabolites in all plant matrices in which residues above LOQ was observed (relevant for all representative uses evaluated; see Section 1).
- Assessment of the extraction efficiency of the monitoring method for bixlozone residues in high water content commodities (relevant for all representative uses evaluated; see Section 1).
- Addressing efficiency of the hydrolysis step used in the method for determination of 5-hydroxy-bixlozone conjugates in animal products (relevant for all representative uses evaluated; see Section 1).
- An ILV of the method for monitoring of 5-hydroxy-bixlozone conjugates in animal products (relevant for all representative uses evaluated; see Section 1).
- Submission of the final study report containing the fourth field trial conducted in rotational crops (relevant for all representative uses, see Section 3).
- Further data were not available to address the risk to honeybees from sublethal effects (relevant for all representative uses, see Section 5).

ABBREVIATIONS

AAOEL	acute acceptable operator exposure level
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AMA	Amphibian Metamorphosis Assay
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight

EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
EMDI	estimated maximum daily intake
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	fish short-term reproduction assay
GAP	Good Agricultural Practice
HPG	hypopharygeal glands
HQ	hazard quotient
$HQ_{contact}$	hazard quotient for contact exposure
HR	hazard rate
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for
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
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
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RAC	regulatory acceptable concentration
SC	suspension concentrate
SD	standard deviation
SMILES	simplified molecular-input line-entry system
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
TWA	time-weighted average
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

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REQUESTOR

European Commission

QUESTION NUMBER

EFSA-Q-2018-00692

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

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

Properties		Conclusion
CMR	Carcinogenicity (C)	Bixlozone is not considered to be a carcinogen (category 1A or 1B) according to point 3.6.3 of Annex II of Regulation (EC) No 1107/2009, based on ECHA RAC opinion (June 2023)
	Mutagenicity (M)	Bixlozone is not considered to be a mutagen according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009, based on ECHA RAC opinion (June 2023)
	Toxic for Reproduction (R)	Bixlozone is not considered to be toxic for reproduction according to point 3.6.4 of Annex II of Regulation (EC) No 1107/2009, based on ECHA RAC opinion (June 2023)
Endocrine disrupting properties		Bixlozone 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**	Bixlozone 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**	Bixlozone is considered to be a persistent (P) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009 Bixlozone is not considered to be a bioaccumulative and toxic (BT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009
vPvB	**Persistence** **Bioaccumulation**	Bixlozone 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

APPENDIX B

List of end points for the active substance and the formulation for representative uses

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2024.9054

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[18] 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.

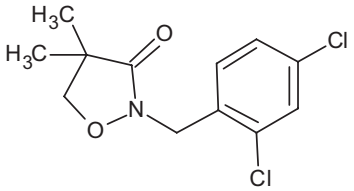
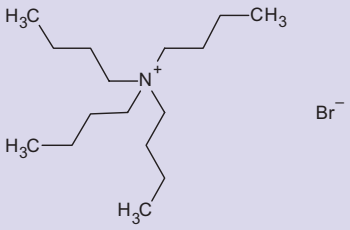
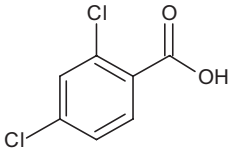
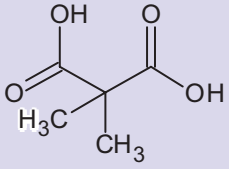
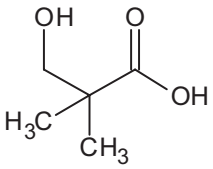
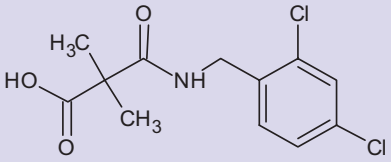
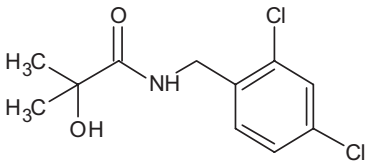
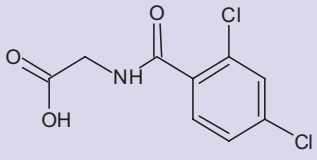
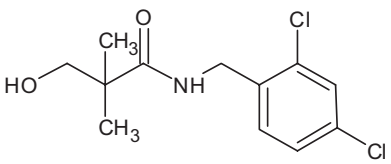
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2000
Slight mobility	2001–5000
Immobile	> 5000

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

[18] 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.

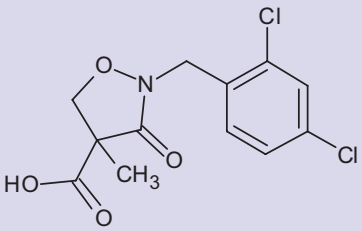
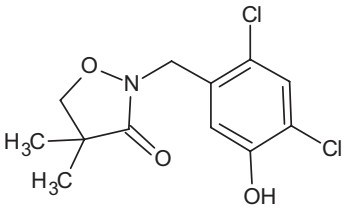
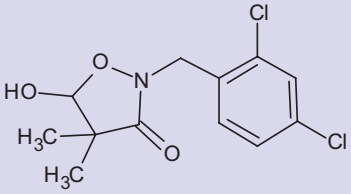
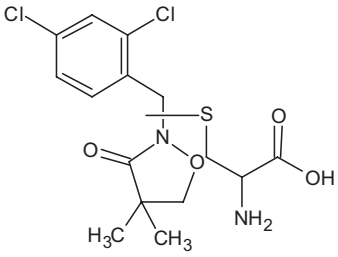
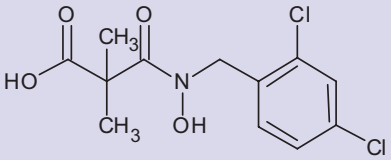
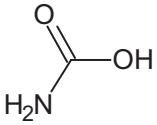
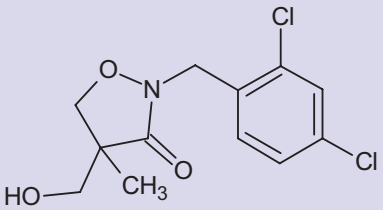
APPENDIX D

Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Bixlozone **F9600**	2-(2,4-dichlorobenzyl)-4,4-dimethylisoxazolidin-3-one CC1(C)CON(Cc2ccc(Cl)cc2Cl)C1 = O FHUKASKVKWSLCY-UHFFFAOYSA-N	
***N,N,N*-tributylbutan-1-aminium bromide** **TBAB**	*N,N,N*-tributylbutan-1-aminium bromide [Br-].CCCC[N+](CCCC)(CCCC)CCCC JRMUNVKIHCOMHV-UHFFFAOYSA-M	
2,4-dichlorobenzoic acid (2,4 DCBA) M190/1	2,4-dichlorobenzoic acid Clc1cc(Cl)ccc1C(O) = O ATCRIUVQKHMXSH-UHFFFAOYSA-N	
Dimethylmalonic acid M132/1	dimethylpropanedioic acid OC(=O)C(C)(C)C(O) = O OREAFAJWWJHCOT-UHFFFAOYSA-N	
2,2-dimethyl-3-OH-propionic acid 2,2-Dimethyl-3-hydroxypropionic acid M118/1	3-hydroxy-2,2-dimethylpropanoic acid OC(=O)C(C)(C)CO RDFQSFOGKVZWKF-UHFFFAOYSA-N	
F9600-dimethyl-malonamide F9600-Dimethylmalonamide Dimethylmalonamide-F9600 M289/2	3-{[(2,4-dichlorophenyl)methyl]amino}-2,2-dimethyl-3-oxopropanoic acid CC(C)(C(=O)O)C(=O)NCc1ccc(Cl)cc1Cl LBOINGBWRXKBKY-UHFFFAOYSA-N	
F9600-hydroxy-isobutyramide M261/1	*N*-[(2,4-dichlorophenyl) methyl]-2-hydroxy-2-methylpropanamide	
2,4-dichlorohippuric acid	*N*-(2,4-dichlorobenzoyl)glycine O=C(NCC(O) = O)c1ccc(Cl)cc1Cl NSEWCAZRGRZTHU-UHFFFAOYSA-N	
F9600-3-OH-propanamide **3-hydroxypropanamide-F9600** M275/1	*N*-[(2,4-dichlorophenyl) methyl]-3-hydroxy-2,2-dimethylpropanamide CC(C)(CO)C(=O)NCc1ccc(Cl)cc1Cl GUGQYAOXJQBYLF-UHFFFAOYSA-N	

(Continues)

(Continued)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
4-carboxyl F9600	2-[(2,4-dichlorophenyl)methyl]-4-methyl-3-oxo-1,2-oxazolidine-4-carboxylic acid OC(=O)C1(C)CON(Cc2ccc(Cl)cc2Cl)C1=O LBZKFGGPGHKDJT-UHFFFAOYSA-N	
5′-Hydroxy-F9600 5′-OH-F9600 M289/3	2-[(2,4-dichloro-5-hydroxyphenyl) methyl]-4,4-dimethyl-1,2-oxazolidin-3-one CC1(C)CON(Cc2cc(O)c(Cl)cc2Cl)C1=O RMOSHMUNCBVLBF-UHFFFAOYSA-N	
5-Hydroxy-F9600 5-OH-F9600 M289/1	2-[(2,4-dichlorophenyl) methyl]-5-hydroxy-4,4-dimethyl-1,2-oxazolidin-3-one CC1(C)C(O)ON(Cc2ccc(Cl)cc2Cl)C1=O LYHIJBPHZIAHOV-UHFFFAOYSA-N	
F9600-cysteine derivative	Structure undefined, a unique name/SMILES/InChiKey cannot be allocated	
5-keto-hydrate-F9600	3-{[(2,4-dichlorophenyl)methyl](hydroxy)amino}-2,2-dimethyl-3-oxopropanoic acid CC(C)(C(O)=O)C(=O)N(O)Cc1ccc(Cl)cc1Cl ZOKBWCBQTOXXNN-UHFFFAOYSA-N	
carbamic acid	carbamic acid OC(=O)N KXDHJXZQYSOELW-UHFFFAOYSA-N	
4-hydroxymethyl-F9600 M289/4	2-[(2,4-dichlorophenyl)methyl]-4-(hydroxymethyl)-4-methyl-1,2-oxazolidin-3-one O=C1N(Cc2ccc(Cl)cc2Cl)OCC1(C)CO KZYNJSJRUJGKGV-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).