CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State Italy and co-rapporteur Member State the United Kingdom for the pesticide active substance metiram 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 metiram as a fungicide on grapes (wine table) and potatoes (all being field uses). It was concluded that following the guidance on this topic, metiram has endocrine disrupting potential, which is a cut-off criterion for non-approval of an active substance. Considerations are also provided on whether exposure to humans and the environment from the representative use of metiram on potatoes can be considered negligible, taking into account information from the applicant and the European Commission's draft technical guidance on this topic. The information available indicated this exposure was not negligible. 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 reported where identified. An evaluation of data concerning the necessity of metiram as a fungicide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented.

Keywords: metiram, peer review, risk assessment, pesticide, fungicide

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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. Metiram 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), Italy, and co-rapporteur Member State (co-RMS), the United Kingdom, received an application from BASF SE for the renewal of approval of the active substance metiram.

An initial evaluation of the dossier on metiram 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 the European Food Safety Authority (EFSA) in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659.

It has been concluded that metiram meets the cut-off criteria for non-approval, laid down in Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 as amended by Commission Regulation (EU) No 2018/605 concerning endocrine disrupting potential. As part of the renewal procedure, the applicant provided further information aimed at demonstrating that the exposure of humans and the environment to metiram was negligible under realistic conditions for just the use on potatoes. Metiram has therefore been assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009 as amended by Commission Regulation (EU) No 2018/605. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of metiram to control a serious danger to plant health. The evaluation of the data regarding this derogation request is presented in Appendices C and D of this conclusion.

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

The uses of metiram according to the representative uses as a fungicide on grapes (wine, table) and potatoes (all being field uses), as proposed at the European Union (EU) level, result in a sufficient fungicidal efficacy against the target organisms.

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 of **identity, physical and chemical properties and analytical methods.**

In the area of mammalian toxicology, operator, bystander and resident exposure estimates are exceeding the reference values for all representative uses (critical area of concern). One issue not finalised is identified, i.e. the phototoxic potential of metiram. With regard to the **negligible exposure** assessment according to the draft technical guidance on assessment of negligible exposure, no predicted or measured value is below 10% of the (A)AOEL. Furthermore, the margin of exposure towards the critical no observed adverse effect level (NOAEL) is below 1,000 considering the representative use on potatoes (use proposed by the applicant to be assessed in relation to negligible exposure).

In the area of **residues** several data gaps were identified and the residue definition for risk assessment proposed for primary crops applies to rotational crops on a provisional basis. Based on the quantitative information on primary and rotational crops to support the representative uses, potential livestock exposure and carry-over of metiram derived residues in animal matrices cannot be excluded and needs to be reconsidered pending the outcome of the identified data gaps. The consumer dietary risk assessment for the representative uses could not therefore be concluded (issue not finalised). With the preliminary chronic consumer dietary intake calculation an acute intake concern was identified for table grapes and wine grapes when metiram (as EBDC) residues were considered (international estimated short-term intake (IESTI): up to 864% acute reference dose (ARfD) for table grapes (FI child 3 years), up to 281% ARfD for wine grapes (UK adults). A **negligible exposure** to metiram residues considering the representative use on potatoes (use proposed by the applicant to be assessed in relation to negligible exposure) could not be demonstrated.

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level for the representative uses, with the exception that information was not available on the effect of the drinking water treatments processes of ozonation and chlorination on the nature of the ETU and EU residues that might be present in surface water,

when surface water is abstracted for the production of drinking water. This has led to the consumer risk assessment not being finalised. The potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L by metiram and its soil transformation products EBIS, TDIT, ETU and EU were assessed as low for the representative uses assessed.

In the area of **ecotoxicology**, the long-term risk assessment to birds could not be finalised, due to the absence of a valid endpoint covering the most sensitive species. The risk to honey bee larvae could not be finalised due to the absence of a suitable lower tier endpoint or sufficiently robust higher refinement allowing to address the risks to bee brood. A high risk to aquatic organisms was identified for all representative uses. The in-field risk to non-target arthropods other than bees was indicated as high for all representative uses.

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, metiram meets the endocrine disruptors criteria for humans for the T-modality (critical area of concern) while the assessment of the **endocrine disruption potential** of metiram to non-target organisms for EATS-modalities could not be concluded (issue not finalised).

Table of contents

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 (ED) 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 Italy and co-RMS the United Kingdom received an application from BASF SE for the renewal of approval of the active substance metiram. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (the United Kingdom), the European Commission and EFSA about the admissibility. The RMS provided its initial evaluation of the dossier on metiram in the RAR, which was received by EFSA on 2 November 2017 (Italy, 2017). In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, BASF SE, for consultation and comments on 26 February 2018. 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 28 April 2018. 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 agreed between EFSA and the RMS Italy on 26 June 2018. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology. The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table. In addition, in accordance with the provisions of Commission Implementing Regulation (EU) No 2018/1659, following a consultation with Member States in the Pesticides Peer Review Expert meeting 190 (January–February 2019), the applicant was given the opportunity to submit, within a period of 3 months, additional information to address the approval criteria set out in point 3.6.5 and/or point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605[4], and/or documentary evidence demonstrating that metiram may be used such that

[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.

exposure is negligible, or the conditions for the application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met. Subsequently, the applicant provided further information aimed at demonstrating that the exposure of humans to metiram and ETU was negligible under realistic conditions of use. Information with regard to negligible exposure of metiram to the environment was also provided. Metiram has therefore been assessed under the provisions of negligible exposure to satisfy point 3.6.5 of Annex II of Regulation 1107/2009. Furthermore, the applicant requested a derogation under Article 4(7) of Regulation (EC) 1107/2009, submitting evidence regarding the necessity of metiram to control a serious danger to plant health. The evaluation of the data regarding this derogation request is presented in the Appendices C and D of this conclusion. A public consultation on the draft Art 4(7) scientific report and the revised RAR on the ED and negligible exposure assessments made available after the 3-month clock stop was conducted between 1 March 2021 and 1 May 2021. All comments received, including from the applicant and Member States, were collated in the format of a commenting table (on the draft Art 4(7) scientific report) and reporting table (on the revised RAR on the assessment of the endocrine disrupting properties and negligible exposure assessment). 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, including the negligible exposure assessment and the evaluation of the data regarding the necessity of metiram to control a serious danger to plant health which cannot be contained by other available means, took place with Member States via a written procedure in February 2023. 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 uses of metiram as a fungicide on grapes (wine table) and potatoes (all being field uses), as proposed by the applicant. In accordance with Article 12 (2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. In addition, the peer review also provided considerations on whether exposure to humans and the environment from the representative potato use of metiram can be considered negligible, taking into account the European Commission's draft guidance on this topic. An evaluation of data concerning the necessity of metiram as fungicide to control a serious danger to plant health which cannot be contained by other available means, including non-chemical methods is also presented (see Appendices C and D). A list of the relevant end points for the active substance and the formulation is provided in Appendix B. In addition, the considerations as regards the cut-off criteria for metiram 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, 2023), 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 comments received on the applicant's report submitted for the evaluation of data concerning the necessity of metiram to control a serious danger to plant health (May 2020);
- the reporting table (26 June 2018);
- the evaluation table (27 February 2023);
- 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 Art 4(7) scientific report;
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Italy, 2022), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available. It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the 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 the representative uses

There is no ISO common name for zinc ammoniate ethylenebis(dithiocarbamate)-poly[ethylenebis (thiuramdisulfide)] (IUPAC) as it is a mixture.[5] The names 'metiram' and 'metiram-zinc' have been used in the literature, but they have no official status. The formulation for the representative uses for the evaluation was 'BAS 222 28 F', water-dispersible granules (WG) containing 700 g/kg metiram. The representative uses evaluated were foliar spray applications for the control of pathogens such as *Plasmopara viticola*, *Phomopsis viticola*, *Pseudopezicula tracheiphila* and *Guignardia bidwellii* on grape and *Phytophtora infestans* and *Alternaria spp*. on potato. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix B. Data were submitted to conclude that the use of metiram according to the representative uses proposed at EU level results in a sufficient fungicidal efficacy against the target organisms, following the guidance document following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b). A data gap has been identified for a transparent evaluation by the RMS of the search of the scientific peer-reviewed open literature on the active substance and its relevant metabolites, dealing with side effects on health, the environment and non-target species and published within the 10 years before the date of submission of the dossier, to be conducted and reported in accordance with EFSA guidance on the submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009 (EFSA, 2011)

Conclusions of the evaluation

1. Identity, physical/chemical/technical properties and methods of analysis

The following guidance documents were followed in the production of this conclusion: European Commission (2000a,b, 2010).

Metiram is produced as a stabilised technical concentrate (TK). The reference specification from the original approval set a minimum purity of 840 g/kg and ethylene thiourea (ETU) considered as a relevant impurity with a maximum limit of 0.5% of the metiram content. The proposed specification for the renewal is based on batch data from industrial scale production of the TK, batch data of the formulation and QC data of the formulation. EFSA and a MS expressed their reservation regarding using data on the formulation for setting the technical specification. The proposed minimum content of metiram in TK was 880 g/kg, however the maximum content was not provided (data gap; see Section 10). It should be noted that based on the batch data of TK, higher minimum purity could have been proposed. The minimum theoretical calculated purity of the technical material (TC) is 930 g/kg. ETU and formaldehyde are considered as relevant impurities with maximum content of 1 g/kg and 0.06 g/kg in the TK, respectively. It is proposed the reference specification be updated based on the data for the renewal (i.e. higher minimum content of the active substance in the TK, new relevant impurity and setting of the maximum level of the relevant impurity ETU as an absolute amount in the TK). The batches used in the toxicological assessment support both the original and proposed updated reference specification (see Section 2). An assessment of the compliance of batches used in the ecotoxicity tests with the reference specifications (proposed renewal specification or original reference specification) was not available (see Sections 5 and 10). A FAO specification is not available for metiram.

The main data regarding the identity of metiram and its physical and chemical properties are given in Appendix B. However, for the relevant impurity formaldehyde, spectral data (if necessary, for the identification) and information on its content before and after storage of the formulation was not available (data gap, see Section 10).

Adequate methods are available for the generation of data required for the risk assessment. Methods of analysis are available for the determination of the active substance in the technical concentrate and in the formulation and for determination of the relevant impurity ETU in the formulation for representative uses. However, for the relevant impurity formaldehyde method for its analysis in the formulation for representative uses was not available (data gap, see Section 10).

Metiram residue can be monitored as ethylenebis(dithiocarbamate) methyl derivative (Me-EBDC) in food and feed of plant origin by liquid chromatography with tandem mass spectrometry (LC–MS/MS) with limit of quantification (LOQ) of 0.05 mg/kg (expressed as metiram) in all commodity groups

[5] ISO actually states 'appears to be a mixture'.

except the high oil content group for which LOQ is 0.1 mg/kg (expressed as metiram). However, the extraction procedure used for dry, high acid and high oil content commodities was not verified (data gap; see Section 10). A method for determination of metiram residue after conversion to CS_2 is available, however it was not fully validated for monitoring purposes. Metiram residue in food of animal origin can be determined by gas chromatography with mass spectrometry (GC–MS) (after conversion to CS_2) with LOQs of 0.01 mg/kg (expressed as CS_2) in all animal matrices; however, a validated independant laboratory validation (ILV) of this method was not available (data gap; see Section 10). It is noted that extraction efficiency used in the method was not verified (incurred residue samples were not available). A validated monitoring method for determination of metiram as Me-EBDC in food of animal origin was not available.

Metiram and ETU residues in soil and water can be monitored by LC–MS/MS with LOQs 0.05 mg/kg and 0.05 μg/L, respectively. Determination of metiram is done after conversion to Me-EBDC. HPLC–ECD method was submitted for monitoring metiram residues in air, however the method is not fully validated according to the relevant guidance document, therefore a data gap for validated monitoring method in air has been identified (data gap; see Section 10).

ETU residue in urine and plasma can be determined by LC–MS/MS with LOQ of 0.01 mg/kg and 0.05 mg/L, respectively. ETU residue in body tissues can be determined by LC–MS/MS with a LOQ of 0.01 mg/kg.

2. Mammalian toxicity

The assessment is based on the following guidance documents: European Commission (2003, 2012), EFSA (2014, 2017), EFSA PPR Panel (2012) and ECHA (2017) and the available draft Technical Guidance Document on assessment of negligible exposure (European Commission, 2015).

The toxicological profile of the active substance metiram and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 190 in January 2019 and at the Pesticides Peer Review Experts' TC 68 in January 2022.

ETU and formaldehyde are identified as toxicologically relevant impurities and of no concern at the proposed maximum level of 1 g/kg and 0.06 g/kg, respectively. Toxicological batches are considered to be sufficiently representative of the newly proposed and current reference specifications.

Metiram is partially (50%) **absorbed** based on urinary and biliary excretion after oral administration of 5 mg/kg body weight (bw) in rats. Metiram is widely **distributed** (highest concentration in kidney and thyroid), with no evidence for accumulation. It is rapidly and extensively **excreted** via faeces and urine. Metiram is extensively **metabolised**, with ETU found as a major metabolite in rat urine. No human-specific metabolites were found in an *in vitro* comparative metabolism study.

As metiram is rapidly metabolised, the residue definition for body fluids (urine and plasma) should include the major rat metabolite ETU.

Metiram demonstrated low **acute toxicity** by the oral, dermal and inhalation routes. It is neither a skin irritant nor an eye irritant. Metiram is a moderate skin sensitiser and has a notified classification Skin Sens. 1. The peer review considered that the criteria for classification according to Regulation (EC) No 1272/2008 may be met for Skin Sens. 1 (H317). A phototoxic potential was observed in an *in vitro* NRU Phototoxicity Test in Balb/c 3 T3 cells. Further investigation of photogenotoxicity is required (issue not finalised; see Section 9.1).

In the **short-term** dietary studies, the thyroid was the main target organ in rats, mice, dogs and monkeys. The short-term no observed adverse effect level (NOAEL) in mice was 100 mg/kg bw per day based on effects on T4 values observed in the 90-day study. The short-term NOAEL in rats was 23.5 mg/kg bw per day based on effects on body weight, liver weight, thyroid (weight, histopathology, T4 values), reduced grip strength, clinical chemistry parameters observed in the 90-day study. The short-term NOAEL in dogs was 2.6 mg/kg bw per day based on effects on thyroid (weight, histopathology and hormone levels) observed in the 1-year study. The short-term NOAEL in monkeys was 5 mg/kg bw per day, based on effects on thyroid (weight, histopathology and hormone levels) and liver (weight) at higher doses from the 6-month study. Based on effects on thyroid and neuromuscular weakness, the peer review considered that the criteria for classification according to Regulation (EC) No 1272/2008[6] may be met for classification STOT RE 2 (H373).[7]

[6] 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.

[7] Refer to experts' consultation 2.2 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2023).

Metiram was tested for gene mutation (bacterial and mammalian cells) and chromosome aberration (aneugenicity and clastogenicity) and it is considered unlikely to be **genotoxic**.

The **long-term** systemic NOAEL in mice was 24 mg/kg bw per day based on decreased body weight gain and food consumption observed in the 18-month study. Metiram was not carcinogenic in mice at up to the highest doses tested of 79 and 95 mg/kg bw per day in males and females, respectively. In rats, the long-term systemic NOAEL was 3.1 mg/kg bw per day based on effects on skeletal muscles' atrophy in the 2-year study. The NOAEL for carcinogenicity in rats was 3.1 mg/kg bw per day, based on thyroid tumours (follicular adenomas and adenocarcinomas in males) observed in the 2-year study. Based on these findings, the peer review considered that the criteria for classification according to Regulation (EC) No 1272/2008 may be met for classification Carcinogenic Category 2.[8]

In the two-generation **reproductive toxicity** study in rats, the parental NOAEL was 9 mg/kg bw per day based on effects on food consumption, body weight (gain) and thyroid histopathological changes (in males). This NOAEL is not however taking into account the pattern of adverse changes that affected the T-modality. Indeed, when considering the overall WOE in the data set of studies available for metiram, the effects on the thyroid observed at the lowest dose in the two-generation study in the F0 males indicated that the dose of 9 mg/kg bw per day was rather representing a lowest observable adverse dose level (LOAEL) and that thyroid-related changes were not observed in the thyroid-related endpoints at doses of 6 mg/kg bw per day in the 90-day rat study or in any study conducted at lower doses in the data set. Therefore, the dose of 6 mg/kg bw per day should be considered the NOAEL for thyroid-related effects (see Section 6). The reproductive NOAEL was 92 mg/kg bw per day (highest dose) and the offspring NOAEL was 31 mg/kg bw per day based on decreased body weight and changes in thyroid hormone levels in female F1 pups. In the **developmental toxicity** study in rats, the maternal NOAEL was 80 mg/kg bw per day based on reduced food consumption, body weight gain and litter size and weight. In the same study the developmental NOAEL was 80 mg/kg bw per day based on increased litter incidence of displaced testis. In the prenatal toxicity study in rabbits, the maternal NOAEL was 10 mg/kg bw per day based on decreased body weight, food consumption, faecal output and on abortions; the developmental NOAEL was 40 mg/kg bw per day based on reduced litter size and foetal weight concomitantly with severe maternal toxicity.

Based on an **immunotoxicity** study in rats, metiram has no immunotoxic potential. Furthermore, the results of metiram testing in an acute and a repeated-dose **neurotoxicity** study support that is not neurotoxic.

With regard to the toxicological reference values, both the **acceptable daily intake** (**ADI**) and the **acute reference dose** (**ARfD**) are set at 0.026 mg/kg bw, based on the 1-year dog study and applying an uncertainty factor (UF) of 100. Both the **acceptable operator exposure level** (**AOEL**) and **acute AOEL** (**AAOEL**) are 0.013 mg/kg bw per day, based on the same 1-year dog study and applying an UF of 100 and an additional correction factor for limited oral absorption (50%).[9] It is noted that during the previous peer review of metiram (European Commission, 2005), different toxicological reference values were derived: an ADI of 0.03 mg/kg bw per day based on the 2-year rat study, an AOEL of 0.016 mg/kg bw per day based on the 1-year dog study with a correction factor for limited oral absorption (60%); while the ARfD was considered not necessary.

Metiram metabolites are common to the active substance mancozeb and have already been discussed during the mancozeb peer review (EFSA, 2020).[10,11] An extensive set of toxicity studies was provided for **ETU**, a major urinary rat metabolite of both metiram and mancozeb. This metabolite is unlikely to be genotoxic and has a harmonised classification for acute toxicity (Acute Toxicity 4) and developmental toxicity (Reproductive Toxicity 1B). Its ADI and AOEL are 0.002 mg/kg bw per day, while its ARfD and the AAOEL are 0.01 mg/kg bw, (EFSA, 2020). It is noted that the critical target organ for repeated dose toxicity of metiram and ETU is the thyroid (same postulated Mode of Action (MoA)) while different critical effects are observed for acute toxicity of both compounds (see Section 3). Toxicity studies were also provided for imidazolidin-2-one (**EU**), major metabolite of mancozeb. This metabolite is unlikely to be genotoxic and shows a toxicity profile similar to mancozeb. Its ADI and ARfD are 0.06 mg/kg bw per day and 0.37 mg/kg bw, respectively (EFSA, 2020).

[8] Refer to experts' consultation 2.4 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2023).
[9] Refer to experts' consultation 2.9 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2023).
[10] Refer to experts' consultation 2.7 and 2.8 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2023).
[11] Refer to experts' consultation 2.8 and 2.9 in the Report of Pesticides Peer Review Experts' Meeting 190 on mancozeb (EFSA, 2020).

Jaffe's Base, found in crops and livestock matrices, is unlikely to be genotoxic; however, information on repeated dose toxicity was not provided to conclude on the general toxicity profile of this metabolite (data gap; see Sections 3 and 9.1).

Metabolite **M222F001** was found in crops. Genotoxic potential cannot be excluded and information on repeated dose toxicity has not been provided to conclude on the general toxicity profile of this metabolite (data gap; see Sections 3 and 9.1).

Dermal absorption values for 'BAS 222 28F' are 10% for both the concentrate product and the in-use dilution (default value).[12]

The **non-dietary exposure** estimates for the **operators** were calculated with the German model, the UK-POEM and the EFSA model (EFSA, 2014). Predictions with the German model and UK-POEM were higher than with the EFSA model. Only results with the EU-validated EFSA model are reported here. For the use on grape, the lowest estimates are 27% of the AOEL and 231% of the AAOEL (including use of gloves and respiratory protective equipment (RPE) during mixing/loading and application (MLA), and closed cabin during application). For the use on potatoes, the lowest exposure values are 28% of the AOEL and 219% of the AAOEL (including use of gloves and RPE during MLA). Based on a study monitoring the ETU concentrations in the spray dilution until application, the operator exposure estimates to ETU for both uses are exceeding the (A)AOEL. Two exposure studies performed on grapes (also taken into consideration in the EFSA model, 2014) were also included, with operator exposure estimates for metiram below the AOEL and AAOEL (> 10%, including use of coverall and gloves during MLA) in the first one, and above the AOEL and AAOEL (243% and 369% including coverall, gloves and RPE during MLA) in the second study. As a conclusion, the operator exposure estimates are exceeding the (A)AOEL for the use on grapes and potatoes (**critical area of concern**; see Section 9.2).

For the **bystanders and residents**, the predicted exposure estimates for both uses exceed the (A)AOEL based on the EFSA model (critical area of concern; see Section 9.2). For the **workers**, based on EUROPOEM, exposure estimates during potato crop inspection or harvest are below the AOEL with the use of gloves. According to EFSA model, all exposure estimates for re-entry into grapes- or potatoes-treated fields, for metiram and ETU, are above the AOEL. Based on a field study in grapevines, and taking into account the refined DFR value and the use of gloves, the maximum worker exposure estimate is 20% of AOEL for metiram and 29% of AOEL for ETU.

For the assessment of **negligible exposure**, only the representative use on potatoes has been considered. Following the available draft technical guidance (European Commission, 2015), no predicted or measured value is below 10% of the (A)AOEL. Furthermore, the margin of exposure towards the critical NOAEL is below 1,000.

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).

Metiram was discussed at the Pesticides Peer Review Experts' Meeting 191 in January 2019.

The metabolism of metiram in primary crops was investigated in fruit crops (apples), root crops (potatoes) and leafy crops (lettuces) upon foliar application of ^{14}C-ethylene metiram. In whole apple fruit, major part of the applied radioactivity (AR) remained in the surface wash extract (61% of AR) and accounted for 19% AR and 13% AR in peel and pulp, respectively. Metiram and ETU were recovered at levels of 9.4% total radioactive residue (TRR) and 1.8% TRR, respectively along with numerous metabolites (EU, EBIS, *N*-acetyl-EDA, hydantoin, Jaffe's base and EDA) that occurred each at a level < 10% TRR. The remaining radioactivity was characterised mainly by fractions corresponding to unknown compounds (7.6% TRR), polar compounds (5.2% TRR), undefined radioactivity (36% TRR) and up to 13% of the total residues were incorporated into natural constituents of the plants (i.e. sugars, amino acids, lignin, cellulose). In potato pulp and peel, parent metiram was never detected while metabolites EBIS/ETT, ETU, EU and *N*-acetyl-EDA were identified at a level far below 10% TRR. Globally, 75% of the total radioactive residues were characterised as both natural products (creatinine, glycine, etc.) and incorporated into the natural constituents of the pulp and peel (amino acids, starch, cellulose, lignin, etc.). In lettuce, the predominant compounds of the total residues were identified as metiram (46% TRR) and a fraction corresponding to analytically undissociated ETU and/or EU (15% of the TRR). Minor identified metabolites (EBIS, TDIT, etc.) were also found each at a

[12] Refer to experts' consultation 2.10 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2023).

level <5% of the TRR while the rest of the radioactivity was constituted of several unidentified fractions, each occurring at a level < 10% TRR. Despite shortcomings identified regarding the storage time intervals of the samples either not reported or not supported by acceptable storage stability data for metiram and its metabolites, these studies were considered as acceptable to confidently address the metabolism of metiram in all crop categories following foliar treatment. Provided that significant residues of metiram, determined, respectively, as CS_2 and as EBDC were found in the GAP compliant residue trials on grapes, the experts proposed the following options for **the residue definition for monitoring: *'dithiocarbamates (metiram), determined and expressed as CS_2'* and/or *'dithiocarbamates (metiram), determined and expressed as EBDC'***.[13] For risk assessment and in view of the metabolic pattern observed in lettuce with the formation of a significant proportion of ETU/EU, the potential inclusion of ETU and EU besides the parent compound in the residue definition was discussed. Given that residues of EU are recovered at relatively lower levels compared to ETU residue levels in the GAP-compliant grapes and potatoes residue trials and ETU being toxicologically more potent compared to metiram and EU (see Section 2), the **risk assessment residue definition is proposed as *'metiram (determined as EBDC and expressed as metiram) and ETU (combined risk assessment for chronic exposure, separated risk assessment for acute exposure – see Section 2)'*[12] for all categories of crops following foliar treatment** (data gap; see Section 2 on metabolite M222F001). Although metiram and its major soil metabolites exhibited very low to moderate persistence in soil (DT_{90} < 100 days) (see Section 4), confined rotational crop metabolism studies in cereal small grains (wheat), leafy crops (lettuce) and root crops (radish), following bare soil application and soil ploughing (3 N rate) showed that neither the parent metiram nor the metabolites identified in primary crops were detected in any plant grown in rotation. The metabolite M222F001 was however identified in significant proportions in lettuce at 30- and 121-day plant-back intervals (PBIs) (up to 19% TRR – 0.14 mg eq./kg) and in high concentrations in the different wheat plant parts at all PBIs. The major part of the radioactive residues (10–63% of the TRR) was characterised as carbohydrates (glucose, fructose, etc.) suggesting a preferential incorporation of the radioactive residues into natural constituents of the plants. Since the genotoxic potential and general toxicity profile. of M222F001 could not be ruled out (data gap; see Sections 2 and 9.1), the residue definition for risk assessment derived for primary crops should be considered as provisional when assessing residues in rotational crops.

The hydrolysis study conducted with metiram and simulating the standard food processing conditions showed a degradation of metiram into ETU that accounted for up to 52% of the AR at pasteurisation, 88.4% AR at baking/brewing and boiling and was almost completely degraded into ETU (98.6% AR) at sterilisation. The risk assessment residue definition set for primary crops also applies to processed commodities.

Shortcomings were noted in the reporting of the storage stability data for **metiram residues determined as CS_2** in white grapes and potatoes. A data gap is therefore set either for a complete data reporting in accordance with the current OECD test guidelines (procedural recoveries, uncorrected aged recoveries at each sampling point) or new guideline-compliant studies addressing the storage stability of metiram (determined as CS_2) in crops representative, respectively, of the high acid content and high starch content commodities and covering the maximum storage time interval of the residue samples of the grapes and potatoes residue trials (data gap; see Section 9.1). Storage stability data were provided for **metiram residues determined as EBDC** in matrices representative of the high water content commodities only, showing however equivocal results when samples were homogenised with dry ice (acceptable freezer storage stability for up to 24 months in onions while residues were not stable in lettuce and cucumber). A data gap is set to provide guideline-compliant storage stability studies for metiram (determined as EBDC) in crops representative, respectively, of the high acid content and high starch content commodities and covering the maximum storage time interval of the residue samples of the grapes and potatoes residue trials[14] (data gap; see Section 9.1). **ETU** residues are not stable in potatoes and a data gap is set for the submission of complete NEU and SEU residue data sets on potatoes with analysis of ETU immediately after sampling. Frozen storage stability data on ETU in grapes are equivocal and are shown to be strongly dependent of the sample work-up in the residue trials (3 months when the samples were coarsely ground and 3 days only when the samples were finely ground). Since the samples from the residue trials on grapes were considered as finely ground, a rapid degradation of ETU residues is expected, and the results cannot be considered as

[13] Refer to experts' consultation 3.2 in the Report of Pesticides Peer Review Experts' Meeting 191 (EFSA, 2023).
[14] Refer to experts' consultation 3.1 in the Report of Pesticides Peer Review Experts' Meeting 191 (EFSA, 2023).

reliable. Therefore, complete NEU and SEU residue data sets on grapes are required with analysis of ETU immediately after sampling (data gap; see Section 9.1).

The metabolism of metiram in livestock was investigated in laying hens and in lactating goats using the ^{14}C-ethylene-metiram. In poultry, the parent metiram was never detected and metabolite **EU** was predominant in all matrices (from 9% TRR-0.35 mg eq./kg in liver to 34% of the TRR-0.235 mg eq./kg in whole eggs). Minor metabolites (below 10% TRR) were also identified as ETU, Jaffe's Base, EDA, *N*-acetyl-EDA and natural compounds (creatinine, hydantoin, glycine, etc.). Significant fractions of the radioactive residues were found to be incorporated into natural compounds (lipids, proteins) (up to 43% TRR in kidney). In goats, metiram was also extensively degraded and never detected. **Jaffe's Base** was the major compound of the total residues in milk (29% TRR-0.177 mg eq./kg), in kidney (39.6% TRR-1.46 mg eq./kg) and in muscle (11% TRR-0.048 mg eq./kg) while **EU** was identified in significant concentrations in milk (0.035 mg eq./kg), liver (0.179 mg eq./kg), kidney (0.172 mg eq./kg) and muscle (0.041 mg eq./kg). **ETU** was the predominant compound of the total residues in fat only (9% -0.028 mg eq./kg). Besides minor metabolites (< 10% TRR) identified in all matrices, a predominant fraction of the radioactivity was incorporated into naturally occurring components (lactose, lipids and amino acids, etc.). The metabolism of metiram in animal matrices was considered as sufficiently investigated although these studies were not fully guideline compliant (maximum storage time intervals of the residue samples not provided). It is proposed to set **the residue definition for monitoring by default as '*dithiocarbamates (metiram), determined and expressed as CS_2*' and/or '*dithiocarbamates (metiram), determined and expressed as EBDC*'. For risk assessment, the residue definition is proposed provisionally as '*metiram (determined as EBDC and expressed as metiram) and ETU (combined risk assessment for chronic exposure, separated risk assessment for acute exposure – see Section 2)*'** (data gap; see Section 2 on 'Jaffe's Base'). Although being a predominant compound of the total residues in eggs and poultry matrices, EU was not included in the residue definition in view of its much lower toxicological potency compared to metabolite ETU. The inclusion of compound '**Jaffe's Base',** found to be predominant in ruminant milk, kidney and muscle, in the residue definition for risk assessment deserves further consideration. Jaffe's Base' is unlikely to be genotoxic, but its general toxicity was not provided and might need to be addressed following finalisation of the livestock dietary burden, respectively, for metiram (as EBDC) and ETU (data gap; see Sections 2 and 9.1). Also, in absence of processing residue trials on potatoes, processing factors (PF), respectively, for metiram and ETU could not be derived for potato processed matrices that may be fed to livestock. A data gap is therefore set for sufficient processing residue trials analysing for metiram (as EBDC) and ETU in those commodities and within a time interval for which acceptable storage stability is demonstrated for both compounds (data gap; see Section 9.1). Meanwhile as a very conservative approach, the default PFs for the relevant potatoes feed items have been considered in the intake calculation.

Poultry and ruminant feeding studies were conducted with metiram only and analysing for the magnitude of metiram (as CS_2) and ETU residues in milk, eggs and tissues. These studies were not considered as guideline compliant in view of the identified deficiencies to reliably estimate the residue levels of metiram and ETU in products of animal origin. Pending the finalisation of the dietary burden calculation, respectively, to metiram (as EBDC) and ETU residues, new poultry and ruminant feeding studies with metiram (as EBDC) and ETU simultaneously fed to the animals may need to be provided. A potential livestock exposure and carry-over of M222F001 from the rotational crops in animal matrices cannot also be excluded. Overall, a comprehensive livestock exposure assessment cannot currently be finalised considering the identified data gaps (issue not finalised; see Section 9.1).

Fish metabolism studies are not required since neither metiram nor ETU are fat soluble (log $P_{ow} < 3$).

Grapes (wine, table) show melliferous capacity (European Commission, 2018). The data requirement to determine the residues of metiram and ETU in pollen and bee products for human consumption resulting from residues taken up by honeybees from these crops at blossom needs to be addressed (data gap; see Section 9.1).

A preliminary consumer chronic and acute dietary risk assessment was conducted considering, respectively, the residues of metiram, determined as EBDC and residues of ETU in table and wine grapes and in potatoes according to PRIMo rev.3.1. Model. An acute intake concern was identified for table and wine grapes only when metiram residues were considered (IESTI: up to 1113.4% ARfD for table grapes (FI child 3 years), up to 362.2% ARfD for wine grapes (UK adults) The consumer dietary risk assessment has to be regarded as provisional and, in view of all the identified data gaps and finalisation of the livestock exposure assessment, may be considered based on lower end estimates of

exposure. The consumer risk assessment is also not finalised as the effect of the water treatments processes of ozonation and chlorination on the nature of the ETU and EU residues that might be present in surface water, when surface water is abstracted for the production of drinking water, has not been addressed (issue not finalised; see Sections 4 and 9.1).

As for the assessment if the provisions of **negligible exposure** according to Regulation (EC) 1107/2009 are met, considering the draft technical guidance on assessment of negligible exposure (European Commission, 2015), the following can be concluded for the representative use in potatoes (applicant communicated to the RMS the withdrawn of use in grapes as representative use in this respect): according to the available residue trials it cannot be excluded that residues above 0.01 mg/kg occur for metiram when used in potato according to the proposed GAP. Of the two components of metiram residues metiram itself cannot be excluded to exceed 0.01 as in several residue trials a LOQ of 0.05 mg metiram/kg was used and the ETU component is found at levels above 0.01 mg/kg in several trials (max 0.038 mg/kg). It should be noted that ETU component of the metiram residue definition has a higher ED potency than parent metiram (see Section 6). The acceptability of these residue trials for the determination of the residues of metiram (as CS_2) and metiram (as EBDC) is pending the submission of guideline compliant storage stability data covering the maximum storage time intervals of the samples of these trials. Complete NEU and SEU residue data sets, respectively, on potatoes are not available with analysis of ETU immediately after sampling (data gap; see Section 9.1). The residue definition for risk assessment for potential succeeding crops cannot be finalised and there is a data gap to address the genotoxicity and general toxicity of metabolite M222F001 (data gap; see Sections 2 and 9.1). Based on the quantitative information on primary and rotational crops to support the representative uses, potential livestock exposure and carry-over of metiram derived potato residues in animal matrices cannot be excluded and need to be assessed. Therefore, measured residues of metiram (metiram + ETU) should be considered to represent lower end exposure estimates and the consumer exposure assessment is not finalised. Available evidence indicates that exposure to metiram residues considering the representative use on potatoes are exceed the trigger of exposure considered negligible in the terms established by Regulation (EC) 1107/2009 as specified in the draft technical guidance on assessment of negligible exposure (European Commission, 2015).

4. Environmental fate and behaviour

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, metiram exhibited very low to low persistence, forming the major (> 10% AR) compounds EBIS (max. 26% AR), TDIT (max. 14% AR) and ETU (max. 11% AR). EU was also present at levels triggering assessment (> 5% AR, max. 7% AR). These compounds exhibited very low to low persistence, except TDIT which exhibited very low to moderate persistence. Mineralisation of the ethylene ^{14}C radiolabels to carbon dioxide accounted for 25–46% AR after 90–99 days. The formation of unextractable residues (not extracted by methanol or methanol followed by basified water 1% EDTA) for these radiolabels accounted for 38–42% AR after 90–99 days. Metiram exhibited immobility in soil. EBIS exhibited medium to low mobility, TDIT exhibited medium mobility and ETU and EU exhibited very high soil mobility. It was concluded that the adsorption of all these compounds was not pH dependent.

In laboratory incubations in dark aerobic natural sediment **water** systems, metiram exhibited low persistence, forming the major metabolites EBIS (max. 17% AR primarily in water, exhibiting low persistence) and ETU (max. 65% AR primarily in water, exhibiting low to moderate persistence) and at levels triggering assessment EU (max. 7% AR primarily in water, exhibiting very high persistence). The unextractable sediment fraction (not extracted by basified water 1% EDTA) was a sink for the ethylene ^{14}C radiolabels, accounting for 26–57% AR at study end (100–105 days). Mineralisation of these radiolabels accounted for 8–51% AR at the end of the study. The necessary **surface water and sediment exposure assessments** (predicted environmental concentration (PEC) calculations) were carried out for the metabolites EBIS, TDIT, ETU and EU using the FOCUS (2001) step 1 and step 2 approach (version 2.1 of the Steps 1–2 in FOCUS calculator). For the active substance metiram, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available.[15] The step 4 calculations appropriately followed the FOCUS (2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 58–91% spray drift reduction for

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

potatoes and 68–92% spray drift reduction for vines), 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 runoff of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 3.0.0) was appropriately used to implement these mitigation measures in the simulations. FOCUS Step 3 calculations were also provided for EBIS and ETU. FOCUS Step 4 calculations were calculated for EBIS and the grapevine uses mitigating the spray drift route of entry with no spray drift buffers up to 10 m (representing a 71–85% spray drift reduction).

Arithmetically correct PEC surface water values that have drift mitigation greater than 95% (combining buffer zones and nozzles) are available in the RAR but have not been relied on for this conclusion (and have not been included in Appendix B), as using them contravenes the relevant FOCUS (2007) guidance.

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 [15]. The potential for groundwater exposure from the representative uses by metiram and its soil metabolites EBIS, TDIT, ETU and EU 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.

The applicant provided some appropriate argumentation to indicate that metiram, EBIS and TDIT residues in surface water would be below 0.1 μg/L at abstraction points from surface water that would be used for the production of drinking water. However, the available information was assessed as insufficient in relation to the (water) moderately persistent ETU and very highly persistent EU. Therefore, a data gap was identified as the effect of the water treatments processes of ozonation and chlorination on the nature of the ETU and EU residues that might be present in surface water, when surface water is abstracted for the production of drinking water drinking water, has not been addressed. This has led to the consumer risk assessment not being finalised (issue not finalised; see Sections 3 and 9.1).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix B. A key to the persistence and mobility class wording used, relating these words to numerical DT and Koc endpoint values can be found in Appendix E.

5. Ecotoxicology

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

Metiram was discussed at the Pesticides Peer Review Experts' Meeting 192 in February 2019 and at the Pesticides Peer Review Experts' TC 68 in January 2022.

An assessment of the compliance of batches used in the (eco)toxicity tests with the reference specifications (proposed renewal specification or original reference specification) was not available in Volume 4 (data gap; see Section 10).

An acute study for **bird** species was conducted with 'premix BAS 222 29 F' (purity 95%) additionally, long term studies with the bobwhite quail and mallard duck were performed with 'BAS 222 28 F' (metiram purity 71.12%) and 'TK BAS 222 29 F' (purity 95%), respectively. The formulations were considered informative of the risk assessment, as reported below.

Based on the available data and risk assessment, a low acute risk for birds of metiram was concluded for all representative uses at the screening step (grape) or Tier-I (potato).

A long-term study testing metiram on mallard duck was available. The dose-dependent reduction of fertility and increased embryonic mortality observed in this study were discussed at the meeting.[16] Overall, experts agreed that no no observed effect level (NOEL) could be set from this study. The use in risk assessment of a pulsed exposure study with the mallard duck using 'TK BAS 222 29 F' was also discussed.[17] While experts agreed on the general validity of the study, they observed a major drawback related to the timing of bird exposure, which did not cover egg-laying. As this phase was deemed potentially crucial, experts disagreed with the use of this study in risk assessment. A long-term study with the bobwhite quail was also available. However, this latter species was not indicated as the most sensitive one. Therefore, the majority of experts agreed that the endpoint from this study was not suitable to address the long-term risks of metiram to birds (issue not finalised; see

[16] Refer to experts' consultation 5.3 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[17] Refer to experts' consultation 5.1 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).

Section 9.1). The RMS did not support this decision. The available higher tier studies, which were originally proposed for use in the long-term risk assessment for birds were discussed at the meeting[18] for consideration at the national level.

Acute studies with the metabolite ETU were available for the zebra finch and the bobwhite quail. Using the geometric mean from these studies, low acute risk to birds was indicated.

Long term studies with ETU were conducted using the mallard duck and bobwhite quail. Using the lowest endpoint derived for the bobwhite, a low chronic risk of ETU to birds was indicated for all representative uses.

For wild **mammals**, two acute studies in rat with the active substance were submitted. Using the geometric mean LD_{50} from these studies, low acute risk to metiram was concluded for all representative uses.

The long term endpoint for wild mammals was derived from the rat two generation study, considering bodyweight effects and decreased food consumption in the F0 and F1 generations. Using this endpoint, a chronic risk at Tier-I to metiram was identified for potatoes (small omnivorous and small and large herbivorous mammals); grapes early and late applications (small herbivorous mammals).

The higher tier risk assessment considered the following refinements: (i) residue decline data for metiram in plants and (ii) arthropods; (iii) deposition factors for food items in grapes and potatoes; (iv) specific focal species; (v) ecological data (proportion of an animal's daily diet obtained in habitat treated with pesticide (PT) and composition of diet obtained from treated area (PD)); (vi) food intake rate (FIR).

The residue decline refinement for metiram was discussed and agreed upon at the Pesticides Peer Review meeting.[19]

After consideration of the aforementioned refinements, a low chronic risk to metiram was identified for the large herbivorous mammals and small omnivorous mammals, while a high risk was still identified for small herbivorous mammals for all representative uses. However, a long-term field study to assess potential impact of metiram on populations of the common vole was available, which was considered to address the risk to small herbivorous mammals for the representative uses in potatoes and grapes.

The risk to birds and wild mammals from exposure to metiram and ETU through drinking water was indicated as low.

Acute oral toxicity studies with ETU were available in rat, mouse and hamster. Using the geometric mean LD_{50} of the three species, a low acute risk to mammals from exposure to ETU was concluded for all representative uses.

The long-term endpoint for ETU for wild mammals was agreed at the expert meeting.[20] Using this endpoint and experimentally derived residue values, which were also discussed at the meeting[21] a low risk for ETU to wild mammals could be concluded for all representative uses, except for small herbivorous mammals. However, the field study with metiram addressing the risk to small herbivorous mammals for metiram could cover ETU.

Acute fish studies with 'BAS 222 28 F' and 'BAS 222 29 F' were conducted using several fish species (i.e. *Oncorhynchus mykiss*, *Cyprinodon variegatus*, *Cyprinus carpio*, *Gasterosteus aculeatus*, *Lepomis macrochirus*, *Leuciscus idus melanotus*, *Pimephales promelas* and *Salvelinus fontinalis*). The lowest endpoint for the parent was derived from a study with *Oncorhynchus mykiss*.

Acute fish studies with the metabolites EU and ETU were also available, while QSAR modelling was used to estimate the acute toxicity of fish of the metabolites TDIT and EBIS.

Long-term fish studies were carried out using 'BAS 222 28 F' and 'BAS 222 29 F' with *Oncorhynchus mykiss* (using juvenile fish, 5-month old) and *Pimephales promelas* (early life stage study), respectively, with the latter resulting in a lower endpoint. A modified exposure study with *Oncorhynchus mykiss* was also available, which was discussed at the experts' meeting.[22] The design of this latter study was considered in principle valid, and the exposure regime was deemed to cover the predicted FOCUS profiles. However, the study was not performed using animals in their early life stages, which was considered a major source of uncertainty. Therefore, the modified exposure study

[18] Refer to experts' consultation 5.2 and 5.4 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[19] Refer to experts' consultation 5.2 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[20] Refer to experts' consultation 5.5 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[21] Refer to experts' consultation 5.4 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[22] Refer to experts' consultation 5.7 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).

was deemed unsuitable for the derivation of a Tier-IIc RAC. Moreover, the experts agreed that the available early life stage test with *Pimephales promelas* was appropriate for the Tier-I chronic risk assessment for fish.

Acute invertebrate studies with 'BAS 222 28 F' or 'BAS 222 29 F' were available for *Americamysis bahia*, *Crassostrea virginica*, *Chydorus sphaericus*, *Physa acuta, Simocephalus vetulus, Cyclopoida* and *Ostracoda*. Additionally, three studies with *Daphnia magna* were submitted, which were discussed and considered suitable for risk assessment by the experts.[23] Acute invertebrate studies were also available for the metabolites EU, ETU and TDIT, while QSAR estimates were provided for EBIS. An acute study comparing the toxicity of unfiltered, filtered and aged 'BAS 222 28 F' solutions to *Daphnia magna* was also available.

Two **long-term invertebrate** studies with 'BAS 222 28 F' and 'BAS 222 29 F' were presented on *Daphnia magna*. Additionally, a life-cycle toxicity study on *Americamysis bahia* was considered acceptable for risk assessment by the experts.[24] Additionally, the Tier-I data showed that *Americamysis bahia* was likely more sensitive than *Daphnia magna*. For the metabolites, a long-term invertebrate study was only available for ETU.

Two pulsed exposure studies with *Daphnia magna* using 'BAS 222 28' were available. The pulse exposure design was discussed at the experts' meeting,[11] where it was considered unsuitable to address risks to aquatic invertebrates, considering that an overall higher sensitivity of *Americamysis bahia* was indicated by Tier-I data.

The toxicity to **sediment dwelling** organisms was investigated using *Chironomus riparius* in a long-term study with the formulation 'BAS 222 28 F' for representative uses. This study was deemed invalid by the experts[25] who considered the results of the analytical verification of metiram residues in the test medium as a major source of uncertainty. Nevertheless, the test was qualitatively considered to indicate that chironomids may be less sensitive to metiram than daphnids. A sub-chronic, spiked sediment study on *Leptocheirus pulmulosus* was available but considered as supplementary information. Therefore, a valid study with sediment dwelling organisms with metiram was not available (data gap; see Section 10).

Algal toxicity studies with 'BAS 222 28 F' were available on *Raphidocelis* (*Pseudokirchneriella*) *subcapitata*, *Navicula pelliculosa* and *Skeletonema costatum*. Additionally, studies with EU and ETU on *Raphidocelis* (*Pseudokirchneriella*) *subcapitata* were available, while QSAR modelling was used to estimate the acute toxicity of TDIT and EBIS to algae.

Studies on *Lemna gibba* were available for 'BAS 222 29 F' and ETU, while no study investigating the toxicity to **aquatic macrophytes** was submitted for the other metabolites.

A mesocosm study with 'BAS 222 28 F' was also discussed at the experts' meeting,[26] where major uncertainties were identified on: (i) the analytical confirmation of the exposure profile; (ii) the absence of raw data and (iii) the power analysis. Overall, the study was not considered sufficiently robust for risk assessment consideration.

The risk assessment for **aquatic organisms** (see Table 1 for further details on the outcome at FOCUS step 3) was driven by the endpoint from the chronic crustacean study with *Americamysis bahia*. Using this endpoint and based on FOCUS 3 exposure estimates, a high chronic risk for aquatic organisms was identified for all representative uses of metiram. This risk could not be mitigated at FOCUS step 4 by implementing measures comparable to a 20-m non-spray buffer zone for any of the representative uses (critical area of concern; see Section 9.2).

Using experimentally derived endpoints or QSAR estimates (see above), a risk assessment for the relevant metabolites in surface water (i.e. EU, ETU, TDIT and EBIS, see Table 2) was conducted. A low acute risk was concluded at FOCUS Step 1–2 for all representative uses, except for EBIS, which indicated high acute risk for fish and invertebrates for the representative use in grapes (late applications) at FOCUS Step 3. This risk could be mitigated at FOCUS step 4 by using measures (e.g. 10-m no-spray buffer zones or a combination of 5-m no-spray buffer zones and 50% drift reducing nozzles). An assessment addressing the long-term risks for fish, invertebrates (acute and chronic), algae and macrophytes was only available for ETU (data gap; see Section 10).

The long-term risk assessment for fish, invertebrates (except ETU), macrophytes (except ETU) and sediment dwellers was not addressed (data gap; see Section 10).

[23] Refer to experts' consultation 5.8 in the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[24] Refer to experts' consultation 5.9 of the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[25] Refer to experts' consultation 5.10 of the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).
[26] Refer to experts' consultation 5.6 of the Report of Pesticides Peer Review Meeting 192 session 1 (EFSA, 2023).

New acute (oral and contact) and chronic studies on adult **honey bees** were conducted with the formulation for representative uses ('BAS 222 28 F' containing 70% metiram, nominally). Acute contact and oral studies with the honey bee were also available for 'BAS 222 28 F' (containing 80% metiram, nominally). Upon submission of additional information by the RMS, these latter studies were invalidated by EFSA considering that the performance of the positive control did not comply with OECD validity criteria.

The available chronic toxicity study with honey bee workers was discussed and deemed valid at the experts' meeting.[27] The tiered risk assessment for honey bee larvae was discussed at the experts' meeting.[28] An acute larval study conducted with the formulation for representative uses was available, which yielded a lower endpoint than the acute study on honeybee workers conducted with the same test item. Therefore, while this evidence was considered an indication of potentially higher sensitivity of larvae compared to workers, the experts agreed to question the use of the larval study in risk assessment, considering the uncertainty related to the acute (i.e. not repeated) exposure regime. A semi-field study investigating effects on honey bee larvae was also available. Its use in risk assessment was discussed, with reference to the decrease in the average brood abundance and the increase in the termination-rate, compared to the control. These effects, although not statistically confirmed, were not dismissed by the experts. Therefore, the test was considered not to address the risks to honey bee larvae (issue not finalised; see Section 9.1).

The acute oral and contact risks for honey bee adults from the representative uses were low according to European Commission (2002a). Additionally, a risk assessment for chronic risk to adult honey bees was conducted according to EPPO (2010), based on which the RMS concluded low risk. However, a risk assessment for adult honey bees for metiram conducted in accordance with EFSA (2013) was not available (data gap; see Section 10).

Similarly, a risk assessment according to EFSA (2013) for metabolites occurring in pollen and nectar was not provided (data gap; see Section 10), and suitable assessment of accumulative and sublethal effects on bees (e.g. hypopharyngeal glands) was not available (data gap; see Section 10).

Furthermore, no risk assessment was performed to address the oral exposure via contaminated surface water and guttation (data gap; see Section 10). Acute contact and oral toxicity studies conducted with the formulation for representative uses with **bumble bees**, but not **solitary bees** were available. However, no risk assessment was performed for non-*Apis* bees.

The toxicity to **non-target arthropods** (NTAs) other than bees was investigated using 'BAS 222 28 F'. Specifically, Tier-I data on the two indicator species *Typhlodromus pyri* and *Aphidius rhopalosiphi*, were available. Extended laboratory and aged residue tests were submitted, covering a total of six arthropod species (*T. pyri*; *A. rhopalosiphi*; *Chrysoperla carnea; Pardosa* spp.; *Orius laevigatus* and *Trichogramma cacoeciae*). Field studies with the formulation for representative uses were carried out in grape (n = 2 in DE; n = 2 in IT) and apple (n = 4 in DE; n = 2 in IT). A meta-analysis of a subset of these field studies was also submitted.

The in-field risk assessment was characterised at Tier-I using default or refined multiple application factors (MAFs) based on foliage DT_{50} (grapevine) and soil DT_{50} (potato – soil exposure). In both cases a high in-field risk was concluded for *T. pyri*. For the off-field areas, Tier-II data were considered more relevant than Tier-I data to address the risks to NTAs, as only the former investigated reproductive effects.

The risk assessment for NTAs was discussed at the experts' meeting,[29] where the following conclusions were drawn:

For the **in-field** exposure, a quantitative risk assessment for soil dwelling NTAs for the use in potato was deemed covered by the foliar dwellers, considering the low soil persistence of metiram. The available Tier-II studies were considered insufficient to demonstrate low in-field risk to NTAs. Two of the field studies in grape were discarded due to the low compliance of the application pattern with the GAP. Concerning the remaining field data in grape and apple, major uncertainties (e.g. use of pesticides other than metiram, power analysis, taxonomy) were identified. Based on the individual field studies and meta-analysis, effects on NTAs in-field due to the representative uses of metiram could not be excluded. Furthermore, despite some studies presenting evidence of recovery within one year, the data set was ultimately considered insufficiently robust to demonstrate recovery. Overall, the experts

[27] Refer to experts' consultation 5.11 in the Report of Pesticides Peer Review Meeting 192 (EFSA, 2023).
[28] Refer to experts' consultation 5.12 in the Report of Pesticides Peer Review Meeting 192 (EFSA, 2023).
[29] Refer to experts' consultation 5.13 in the Report of Pesticides Peer Review Meeting 192 (EFSA, 2023).

concluded high in-field risk for NTAs for all representative uses (critical area of concern; see Section 9.2).

The off-field risk assessment was also agreed upon at the experts' meeting[22], and a high risk was indicated. This risk could be mitigated by implementing measures such as 5 and 15-m no-spray buffer zones for potatoes and grapes, respectively.

Chronic **earthworm** studies were conducted with 'BAS 222 28 F' and relevant soil metabolites TDIT (M222F007); ETU (M222F002); EU (M222F003); EBIS (M222F004). Further tests on **other soil macroorganisms** *Folsomia candida* (i.e. 'BAS 222 28 F' and ETU) and *Hypoaspis aculeifer* (i.e. 'BAS 222 28 F') were submitted. No data on other relevant soil metabolites (i.e. EU, EBIS and TDIT) were submitted for these species. However, an illustrative risk assessment assuming they are 10 times more toxic than the parent showed that the risks were low for all representative uses. Based on these data, a low risk for soil macroorganisms was concluded at Tier-I for both metiram and its relevant soil metabolites for all representative uses.

Data on **soil microorganisms** were conducted with 'BAS 222 28 F', ETU (M222F002) and EU (M222F003). No study investigating the toxicity to soil microorganisms of TDIT and EBIS was available. Considering the short DT_{50} of EBIS (usually $<$ 1 day) and considering its peak formation is shortly after application, its risk assessment is considered covered by investigations with 'BAS 222 28 F'.

Based on the available information, a low risk for soil microorganisms was concluded at tier-I for metiram and all relevant soil metabolites, except TDIT (data gap; see Section 10) for all representative uses.

Vegetative vigour and seedling emergence tests were submitted and the risk to **non-target terrestrial plants** was assessed as low for all the representative uses.

For the **biological methods in sewage treatment plants** an activated sludge study was submitted, based on which low risk was concluded.

Table 1: Risk Assessment for aquatic organisms following the representative uses of metiram at FOCUS Step 3

Use		Fish		Invertebrates		Algae[(d)]	Macrophytes	Sediment-dwelling
		Acute[(a)]	Chronic	Acute[(b)]	Chronic[(c)]			
Grape	2 × 0.84 kg a.s./ha (BBCH 05–19)	Low	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	**High** (3/5 scenarios: d6, r2, r3)	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	Low	No valid endpoint was available (data gap). However, qualitative evidence suggests lower sensitivity of chironomids compared to daphnids.
	3 × 1.4 kg a.s./ha (BBCH 53–79)	Low	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	**High** (5/5 scenarios: d6, r1, r2, r3, r4)	Low	
Potato	1 × 1,440 g a.s./ha (BBCH 21–89)	Low	**High** (6/6 scenarios: d3, d4, d6, r1, r2, r3)	**High** (6/6 scenarios: d3, d4, d6, r1, r2, r3)	**High** (6/6 scenarios: d3, d4, d6, r1, r2, r3)	**High** (6/6 scenarios: d3, d4, d6, r1, r2, r3)	Low	

BBCH: Biologische Bundesanstalt, Bundessortenamt and CHemical; a.s.: active substance.
(a): Based on HC_5 = 0.097 mg a.s./L (fish acute SSD) and assessment factor of 3.
(b): Geometric mean EC_{50} = 3.81 mg/L, considering the following species: *D. magna* (geomean of 3 studies), *C. spharicus, Cyclopoida sp., S. vetulus* and *A. bahia*.
(c): Based on NOEC = 0.00157 mg a.s./L (*A. bahia*).
(d): Based on ErC_{50} = 0.007 mg a.s./L (*S. costatum*).

Table 2: Risk Assessment for aquatic organisms for the relevant metabolites of metiram

Metabolite	Use		Fish		Invertebrates		Algae	Macrophytes	Sediment dwellers
			Acute	Chronic	Acute	Chronic			
EU	Grape	2 × 0.84 kg a.s./ha (BBCH 05–19)	Low	n/a	Low	n/a	Low	n/a	n/a
		3 × 1.4 kg a.s./ha (BBCH 53–79)	Low	n/a	Low	n/a	Low	n/a	n/a
	Potato	1 × 1,440 g a.s./ha (BBCH 21–89)	Low	n/a	Low	n/a	Low	n/a	n/a
ETU	Grape	2 × 0.84 kg a.s./ha (BBCH 05–19)	Low	n/a	Low	Low	Low	Low	n/a
		3 × 1.4 kg a.s./ha (BBCH 53–79)	Low	n/a	Low	Low	Low	Low	n/a
	Potato	1 × 1,440 g a.s./ha (BBCH 21–89)	Low	n/a	Low	Low	Low	Low	n/a

Metabolite	Use		Fish		Invertebrates		Algae	Macrophytes	Sediment dwellers
			Acute	Chronic	Acute	Chronic			
TDIT	Grape	2 × 0.84 kg a.s./ha (BBCH 05–19)	Low[(a)]	n/a	Low	n/a	Low[(a)]	n/a	n/a
		3 × 1.4 kg a.s./ha (BBCH 53–79)	Low[(a)]	n/a	Low	n/a	low[(a)]	n/a	n/a
	Potato	1 × 1,440 g a.s./ha (BBCH 21–89)	Low[(a)]	n/a	Low	n/a	Low[(a)]	n/a	n/a
EBIS	Grape	2 × 0.84 kg a.s./ha (BBCH 05–19)	Low[(a)]	n/a	Low[(a)]	n/a	Low[(a)]	n/a	n/a
		3 × 1.4 kg a.s./ha (BBCH 53–79)	**High**[(a)] (Focus Step 3, 5/5 scenarios: d6, r1, r2, r3, r4)	n/a	**High**[(a)] (Focus Step 3, 3/5 scenarios: d6, r2, r3)	n/a	Low[(a)]	n/a	n/a
	Potato	1 × 1,440 g a.s./ha (BBCH 21–89)	Low[(a)]	n/a	Low[(a)]	n/a	Low[(a)]	n/a	n/a

n/a: not available.
BBCH: Biologische Bundesanstalt, Bundessortenamt and CHemical
(a): Based on QSAR estimates.

6. Endocrine disruption properties

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

The **T-modality** has been considered sufficiently investigated and T-mediated adversity (changes in thyroid weight and changes in thyroid histopathology) and T-mediated endocrine activity (changes in thyroid hormones and thyroid-stimulating hormone (TSH)) have been observed in several species.

Metiram is a member of the ethylene bisdithiocarbamate (EBDC) group of fungicides. The EBDCs share **ethylenethiourea (ETU)** as a common contaminant, metabolite and degradation product. The available data set used for the ED assessment includes studies conducted with metiram alone, ETU alone or with metiram containing spiked ETU. A pattern of T-mediated adverse effects was evident in studies conducted with the three test materials; though at different doses. This difference in potency was mainly assessed in rat, which was indicated as the most sensitive species.

The postulated mode of action (MoA) indicates thyroid peroxidase (TPO) inhibition as a plausible molecular initiating event (MIE). However, there are no studies available investigating the MIE using metiram, but there is enough evidence of TPO inhibition for ETU.

In the studies conducted with metiram, the LOAEL where T-mediated adversity was observed in the form of thyroid histopathology (thyroid follicular cell hypertrophy and hyperplasia in male parental animals) was 9 mg/kg bw day in adult animals in a two-generation study. A NOAEL cannot be derived for this study, but no effects were observed on thyroid weight and/or thyroid histopathology at doses of 6 mg/kg per bw day in the 90-day rat study or in any study conducted at lower doses in the data set.

Studies conducted with ETU alone indicates that no adverse changes (in thyroid histopathology and in thyroid hormones) were observed in the extended one-generation study at 0.2 mg/kg bw day and at 0.27 mg/kg bw day in the two-generation study (only thyroid histological endpoints were assessed). However, in the 24-month rat study, thyroid hyperplasia was observed at 0.25 mg/kg bw day, possibly indicating that the use of 0.2 mg/kg bw day as a NOAEL has uncertainties.

Based on the available and sufficient data set and the MoA analysis, it was concluded that the ED criteria for T-modality are met for metiram (**Scenario 1b** of the EFSA/ECHA (2018) ED Guidance), leading to a critical area of concern (see Section 9.2).

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

The outcome of the assessment for humans for the **T-modality** does not apply to **wild mammals** as **non-target organisms** since the relevance of the T-mediated adversity observed in mammals could not be confirmed at population level (organ parameters only, no apical endpoints). **For EAS-modalities**, the conclusion drawn above for humans (criteria not met) also applies to wild mammals.

For non-target organisms other than mammals, for metiram, neither information on adversity nor on endocrine activity was available to determine if the substance meets the ED criteria for the **T-modality**. A number of studies were available where the endogenous metabolite ETU was dosed to amphibians.

Although all the available studies with **ETU** showed minor to major deficiencies and could not be considered as fully reliable, a consistent pattern of endocrine T-mediated adversity and endocrine activity was observed, i.e. delay in development coupled with changes in thyroid histopathology, when assessed.

Several uncertainties were identified when trying to extrapolate the conclusion reached on ETU to metiram:

- Metabolism studies were not available on non-mammalian vertebrates enabling it to be understood whether a similar metabolic pattern occurs as in mammals, although it is considered likely, at least qualitatively;

- All the available metabolism studies in mammalian vertebrates showed not only that ETU is always formed (below 10%) but also that it is rapidly metabolised;
- It is hypothesised that metiram could have a T-mediated MoA through the formation of ETU; however, data are unavailable with metiram to confirm such an assumption;
- In the available studies with ETU, effects were observed around and above 25 mg/L. This may raise uncertainty on the concentrations of metiram that should be tested in amphibians to elicit an ED adverse effect/endocrine activity when also considering the amount of ETU which may be formed during metabolism.

Therefore, although it is hypothesised that metiram could have a T-mediated MoA through ETU formation, based on the available information and in absence of data to confirm such an assumption, a firm conclusion on whether metiram is an endocrine disruptor through the T-modality could not be drawn.

Sufficient data were not available to perform an ED assessment in line with the ECHA/EFSA ED Guidance for EAS-modalities for non-target organisms.

According to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that metiram meets the ED criteria for humans for the T-modality. Metiram was considered not to meet the ED criteria for EAS-modalities for humans.

Based on the available information on non-target organisms, the assessment of the endocrine disruption potential of metiram for **EATS-modalities** according to points 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, cannot be concluded (issue not finalised; see Section 9.1).

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

Regarding the environment, the available PEC in surface water and sediment for metiram and the representative use on potatoes (use proposed by the applicant to be assessed in relation to negligible exposure) are above levels that can be routinely measured.[30] There will be exposure of metiram via food items of non-target organisms for the representative use on potatoes, as these organisms will enter fields on the same day an application is made.

7. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 3–6)

Table 3: Soil

Compound (name and/or code)	Ecotoxicology
Metiram	Low risk to soil organisms
ETU	Low risk to soil organisms
EU	Low risk to soil organisms
EBIS	Low risk to soil organisms
TDIT	Low risk to soil organisms, except microorganisms

Table 4: 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
metiram	No	Yes	–	–	Yes
ETU	No	Not triggered	Not triggered	No	Not triggered
EU	No	Not triggered	Not triggered	No	Not triggered

[30] In line with the ethos of FAO/WHO (2009) further discussed in EFSA Scientific Committee (2012) and limits of analytical quantification needed for monitoring methods set out in European Commission (2021).

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
EBIS	No	Not triggered	Not triggered	No	Not triggered
TDIT	No	Not triggered	Not triggered	No	Not triggered

(a): Assessment according to European Commission guidance of the relevance of groundwater metabolites (2003).
(b): FOCUS scenarios or a 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 5: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Metiram	High risk for all representative uses
ETU	Low acute risk and low chronic risk to invertebrates and macrophytes. Data gap to address the long-term risk to aquatic organisms (fish and sediment dwellers).
EU	Low acute risk. Data gap to address the long-term risk to aquatic organisms and the risk to sediment dwellers.
EBIS	Low acute risk (FOCUS step 4). Data gap to address the long-term risk to aquatic organisms and the risk to sediment dwellers.
TDIT	Low acute risk. Data gap to address the long-term risk to aquatic organisms and the risk to sediment dwellers.

Table 6: Air

Compound (name and/or code)	Toxicology
Metiram	Rat LC_{50} > 5.7 mg/L air /4 h (nose-only)

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 (Table 7).

Table 7: Risk mitigation measures proposed for the representative uses assessed

Representative use	Grapes foliar spray	Potatoes foliar spray
Operator risk	Use of PPE is required[a]	Use of PPE is required[b]
Worker exposure		Use of gloves is required (EUROPOEM)

(a): For tractor-mounted application (upward): gloves and RPE (MLA) + closed cabin (A) for short-term exposure (%AOEL) (EFSA, 2014).
(b): For tractor-mounted application (downward): gloves and RPE (MLA) for short term exposure (%AOEL) (EFSA, 2014).

9. Concerns and related data gaps

9.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for one or more of the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[31] 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) Phototoxic potential of metiram cannot be concluded (see Section 2).
    a) Further investigation of photogenotoxicity is required (relevant for all representative uses evaluated; see Section 2).
2) The consumer dietary risk assessment could not be concluded in view of the identified data gaps, the provisional residue definition for risk assessment for rotational crops and animal matrices, and the potential livestock exposure and carry-over of metiram-derived residues in animal matrices that cannot be excluded and need to be reconsidered pending upon the outcome of the identified data gaps (see Section 3).
    a) The genotoxic potential and general toxicity of metabolite M222F001 (relevant for the representative use on potatoes evaluated; see Section 2).
    b) No information on repeated dose toxicity has been provided to conclude on the general toxicity profile of the metabolite Jaffe's Base (relevant for the representative use on potatoes evaluated; see Section 2).
    c) Regarding the storage stability data for metiram residues determined as CS_2 in white grapes and potatoes, either a complete data reporting in accordance with the current OECD test guidelines (procedural recoveries, uncorrected aged recoveries at each sampling point) or new guideline-compliant studies addressing the storage stability of metiram (determined as CS_2) in crops representative, respectively, of the high acid content and high starch content commodities and covering the maximum storage time interval of the residue samples of the grapes and potatoes residue trials (relevant for all representative uses evaluated, see Section 3).
    d) Guideline-compliant storage stability studies for metiram (determined as EBDC) in crops representative, respectively, of the high acid content and high starch content commodities and covering the maximum storage time interval of the residue samples of the grapes and potatoes residue trials (relevant for all representative uses evaluated, see Section 3).
    e) Complete NEU and SEU residue data sets on potatoes and grapes with analysis of ETU immediately after sampling (relevant for all representative uses evaluated, see Section 3).
    f) Sufficient processing residue trials analysing, respectively, for metiram (determined as EBDC) and ETU in potato processed commodities and within a time interval for which acceptable storage stability is demonstrated for both compounds (relevant for the representative use on potatoes evaluated, see Section 3).
    g) Determination of the residues of metiram and ETU in pollen and bee products for human consumption resulting from residues taken up by honeybees from these crops at blossom (relevant for all representative uses evaluated, see Section 3).

[31] 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 consumer risk assessment was not 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 metabolites ETU and EU (see Sections 3 and 4).
    a) Satisfactory information was not available to demonstrate that residues that may originate from ETU and EU 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 any substances resulting from water treatment of surface water abstracted for the production of drinking water). In the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. Further information might be provided regarding ETU and EU concentrations at the point of abstraction for drinking water purposes being low. Should this consideration indicate novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them should be addressed (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).
4) The assessment of the long-term risk to birds could not be finalised due to the absence of a valid endpoint covering the most sensitive species (relevant for all representative uses, see Section 5).
    a) The long term toxicity to the most sensitive bird species should be further investigated.
5) The risk to honey bee larvae could not be finalised.
    a) A valid lower tier endpoint carried out following a repeated exposure design was not available (see Section 5).
    b) A suitable, sufficiently robust higher tier study allowing to exclude effects on brood was not available (see Section 5).
6) The available data did not allow to draw a conclusion on the potential endocrine disrupting properties of metiram on non-target organisms through EATS-modalities (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 6).

9.2. Critical areas of concern

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

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

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

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

7) Operator, bystander and resident exposure estimates are exceeding the reference values (relevant for all representative uses evaluated; see Section 2).
8) Metiram meets the ED criteria for humans for the T-modality, according to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 6).

9) A high risk to aquatic organisms was identified for all representative uses (see Section 5).
10) A high in-field risk for NTAs was identified for all representative uses (see Section 5).

9.3. Overview of the concerns identified for each representative use considered (Table 8)

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

In addition to the issues indicated in Table 8 below, metiram is considered to meet the criteria for endocrine disruption for humans for T-modality according to points 3.6.5 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605. For the considerations as regards negligible exposure assessment, please refer to Sections 2, 3, 6 and Appendix B.

Table 8: Overview of concerns reflecting the issues not finalised, critical areas of concerns and the risks identified that may be applicable for some but not for all uses or risk assessment scenarios

Representative use		Grapes	Potatoes
		Foliar spray	Foliar spray
Operator risk	Risk identified	X[7]	X[7]
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Resident/bystander risk	Risk identified	X[7]	X[7]
	Assessment not finalised		
Consumer risk	Risk identified	X (Table/Wine grapes)	
	Assessment not finalised	X[2,3]	X[2,3]
Risk to wild non-target terrestrial vertebrates	Risk identified		
	Assessment not finalised	X[4]	X[4]
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[10]	X[10]
	Assessment not finalised	X[5]	X[5]
Risk to aquatic organisms	Risk identified	X[9]	X[9]
	Assessment not finalised		
Groundwater exposure to active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached		
	Parametric value of 10 µg/L[(a)] breached		
	Assessment not finalised		

The superscript numbers relate to the numbered points indicated in Sections 9.1 and 9.2 Where there is no superscript number, see Sections 3 for further information.
(a): 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:

- Maximum content of metiram in TK (relevant for all representative uses evaluated; see Section 1).

- Extraction efficiency for dry, high acid and high oil content commodities (relevant for all representative uses evaluated; see Section 1).
- Validated ILV of the monitoring method in animal products (relevant for all representative uses evaluated; see Section 1).
- Validated method for monitoring of metiram in air (relevant for all representative uses evaluated; see Section 1).
- For the relevant impurity formaldehyde spectral data (if necessary for the identification) and information on its content before and after storage of the formulation (relevant for all representative uses evaluated; see Section 1).
- For the relevant impurity formaldehyde methods for its analysis in the formulation for representative uses (relevant for all representative uses evaluated; see Section 1).
- A fully valid and reliable study with sediment dwelling organisms such as *Chironomus riparius* was not available (relevant for all representative uses evaluated, see Section 5).
- A risk assessment for bees conducted with EFSA (2013) was not provided for metiram or the metabolites occurring in pollen and nectar. Furthermore, a risk assessment for contaminated water was not provided (relevant for all representative uses evaluated, see Section 5).
- Suitable assessment of accumulative and sublethal effects in bees (e.g. hypopharyngeal glands) was not available (relevant for all representative uses evaluated, see Section 5).
- An assessment of the compliance of batches used in the ecotoxicity tests with the reference specifications (proposed renewal specification or original reference specification) was not available in the Vol. 4 (relevant for all representative uses, see Section 5).
- Studies addressing the long-term risk to aquatic and sediment organisms of EU, ETU (fish and sediment dwellers only) TDIT and EBIS (relevant for all representative uses, see Section 5).
- Information addressing the risks to soil organisms of the metabolite TDIT (relevant for all representative uses, see Section 5).

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Abbreviations

a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
BBCH	Biologische Bundesanstalt, Bundessortenamt and CHemical
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
EC_{50}	effective concentration
ECHA	European Chemicals Agency
EEC	European Economic Community
ErC_{50}	effective concentration (growth rate)
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the United Nations
FIR	food intake rate
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
IESTI	international estimated short-term intake
LV	independant laboratory validation
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_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MoA	mode of action
MRL	maximum residue level
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

NTA	non-target arthropod
OECD	Organisation for Economic Co-operation and Development
PD	proportion of different food types
PEC	predicted environmental concentration
PHI	preharvest interval
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
PT	proportion of diet obtained in the treated area
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
RPE	respiratory protective equipment
SFO	single first-order
SMILES	simplified molecular-input line-entry system
SSD	species sensitivity distribution
TK	technical concentrate
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

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

Properties		Conclusion[(a)]
CMR	Carcinogenicity (C)	According to points 3.6.2 of Annex II of Regulation (EC) 1107/2009, the peer review agreed that the criteria for classification as Carcinogenic Cat.2 might be met.
	Mutagenicity (M)	Metiram is not considered to be a mutagen according to point 3.6.2 of Annex II of Regulation (EC) No 1107/2009.
	Toxic for Reproduction (R)	Metiram is not considered to be toxic for reproduction according to point 3.6.4 of Annex II of Regulation (EC) No 1107/2009.
Endocrine disrupting properties		According to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that metiram meets the ED criteria for humans for the T-modality. Metiram was considered not to meet the ED criteria for EAS-modalities for humans. Based on the available information on non-target organisms, the assessment of the endocrine disruption potential of metiram for EATS-modalities according to points 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, cannot be concluded (issue not finalised; see Section 9.1).
POP	**Persistence**	Metiram is not considered to be a persistent organic pollutant (POP) according to point 3.7.1 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Long-range transport	
PBT	**Persistence**	Metiram is not considered to be a persistent, bioaccumulative and toxic (PBT) substance according to point 3.7.2 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	
	Toxicity	
vPvB	**Persistence**	Metiram is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/2009.
	Bioaccumulation	

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

Appendix B – List of end points for the active substance and the 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.2023.7937

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

Appendix C can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.7937

Appendix D – Data collection set

Validated Excel files submitted by MS and evaluated by EFSA in the context of the assessment of the evaluation of data under Art 4(7) of Regulation (EC) No 1107/2009 concerning the necessity of metiram as fungicide to control a serious danger to plant health which cannot be contained by other available means.

Appendix E – Wording EFSA used in Section 4 of this conclusion, in relation to DT and Koc 'classes' exhibited by each compound assessed

Wording	DT_{50} normalised to 20°C for laboratory incubations[32] 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–< 10 days
Moderate persistence	10–< 60 days
Medium persistence	60–< 100 days
High persistence	100 days to <1 year
Very high persistence	A year or more

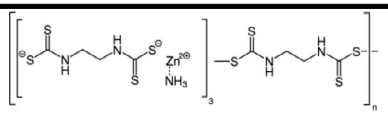
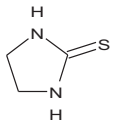
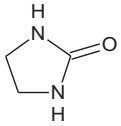
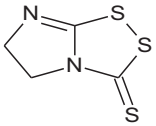
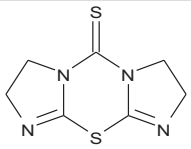
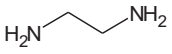
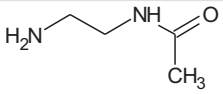
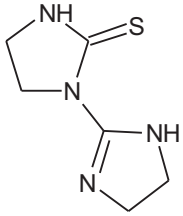
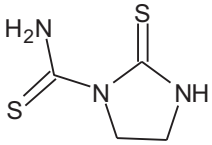
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

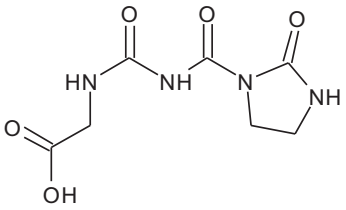
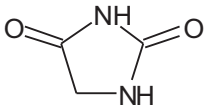
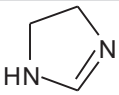
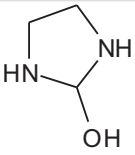
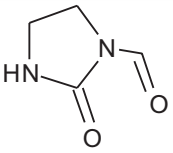
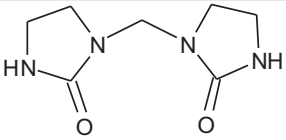
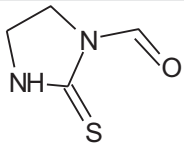
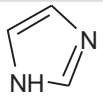
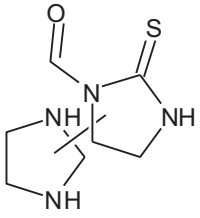
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2,000
Slight mobility	2001–5,000
Immobile	> 5,000

Based on McCall et al. (1980).

[32] 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 F – Used compound codes.

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Metiram	Zinc ammoniate ethylenebis(dithiocarbamate)-poly [ethylenebis(thiuramdisulfide)]	
ETU M222F002 Ethylenethiourea Reg. no. 146099	2-imidazolidinethione S=C1NCCN1 PDQAZBWRQCGBEV-UHFFFAOYSA-N	
EU M222F003 Reg. no. 27270	imidazolidin-2-one O=C1NCCN1 YAMHXTCMCPHKLN-UHFFFAOYSA-N	
EBIS DIDT M222F004 Reg. no. 243959	5,6-dihydroimidazo[2,1-*c*][1,2,4]dithiazole-3-thione S=C1SSC2=NCCN12 BFTGQIQVUVTBJU-UHFFFAOYSA-N	
TDIT M222F007 Reg. No. 4670450	2,3,7,8-tetrahydrodiimidazo[2,1-*b*:1′,2′-*e*][1,3,5] thiadiazine-5-thione S=C1N2CCN=C2SC2=NCCN21 SJPJEYGYJYODMC-UHFFFAOYSA-N	
EDA	ethane-1,2-diamine NCCN PIICEJLVQHRZGT-UHFFFAOYSA-N	
***N*-acetyl-EDA**	*N*-(2-aminoethyl)acetamide CC(=O)NCCN DAKZISABEDGGSV-UHFFFAOYSA-N	
Jaffe's base M222F022 Reg. No. 6002546	1-(4,5-dihydro-1*H*-imidazol-2-yl)imidazolidine-2-thione S=C1NCCN1C=1NCCN=1 LEOYJTSFZDZNJM-UHFFFAOYSA-N	
ETT	2-sulfanylideneimidazolidine-1-carbothioamide NC(=S)N1CCNC1=S CBROQIPVRZGUBN-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
M222F001	*N*-[(2-oxoimidazolidine-1-carbonyl)carbamoyl]glycine O=C1NCCN1C(=O)NC(=O)NCC(=O)O GBFUMICFBCUDRN-UHFFFAOYSA-N	
Hydantoin Reg. No. 132345	imidazolidine-2,4-dione O=C1NC(=O)CN1 WJRBRSLFGCUECM-UHFFFAOYSA-N	
M222F011	4,5-dihydro-1*H*-imidazole C1 = NCCN1 MTNDZQHUAFNZQY-UHFFFAOYSA-N	
M222F012	imidazolidin-2-ol OC1NCCN1 JGVCWPMJYKIFPV-UHFFFAOYSA-N	
M222F013	2-oxoimidazolidine-1-carbaldehyde O=C1NCCN1C=O TUFDCXJCUGHIJH-UHFFFAOYSA-N	
M222F015	1,1′-methylenedi(imidazolidin-2-one) O=C1NCCN1CN1CCNC1=O OYJDFNFZIOOALB-UHFFFAOYSA-N	
M222F016	2-sulfanylideneimidazolidine-1-carbaldehyde S=C1NCCN1C=O SEZXDIZHRQESIV-UHFFFAOYSA-N	
M222F017	1*H*-imidazole c1cnc[NH]1 RAXXELZNTBOGNW-UHFFFAOYSA-N	
M222F018	Structure undefined, a unique name/SMILES/ InChiKey cannot be allocated	

(a): The compound/metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 7 July 2021).
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 August 2021).