CONCLUSION ON PESTICIDES PEER REVIEW

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

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Estonia, and co-rapporteur Member State, Germany, for the pesticide active substance metribuzin and the assessment of application to amend existing residue definition 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 use of metribuzin as a herbicide on potato and soybean (field use). 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.

Keywords: metribuzin, peer review, risk assessment, pesticide, herbicide

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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. Metribuzin is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), Estonia, and co-rapporteur Member State (co-RMS), Germany, received an application from Task Force Metribuzin (consisting of Bayer AG and ADAMA Agan Ltd.) for the renewal of approval of the active substance metribuzin. In addition, Task Force Metribuzin submitted an application to amend an existing residue definition.

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

The uses of metribuzin according to the representative uses as a herbicide by field spray application on potato and soybean, as proposed at EU level result in a sufficient herbicidal efficacy against the target weeds.

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

In the area of **mammalian toxicology**, a critical area of concern was identified as non-dietary exposure estimates exceeded the A(AOEL) value for bystanders and residents for all representative uses evaluated.

In the area of **residues**, the residue definitions for plant and animals could not be finalised due to missing toxicological data on DK-metribuzin and sufficient number of residue field trials with potato and soybean. Consequently, the dietary burden and the consumer risk assessment could not be finalised. The maximum residue level (MRL) requests were not supported by the sufficient data. However, it should be noted that when considering the new toxicological reference values for metribuzin and only the residues from the four valid residue field trials with potato (all below LOQ of 0.01 mg/kg), the acute risk is already 77% of the acute reference dose (ARfD) (potato, UK infant).

The data available on **environmental fate and behaviour** are sufficient to carry out the required environmental exposure assessments at EU level, with the notable exception that a data gap was identified for information on the effect of water treatment processes on the nature of residues potentially present in surface water and groundwater, when surface water and groundwater are abstracted for the production of drinking water. This gap leads to the consumer risk assessment from the consumption of drinking water being not finalised for all the representative uses. Furthermore, an issue not finalised was identified for the potential groundwater contamination by metabolites DK-metribuzin, DADK-metribuzin and 4-methyl-DADK-metribuzin.

In the area of **ecotoxicology**, low risk to birds, mammals, aquatic and soil organisms was concluded. High risk to bees for all representative uses could not be excluded and a critical area of concern was identified for bees. High in-field risk to non-target arthropods was identified for the representative uses on potato.

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) 2018/60, it can be concluded that metribuzin meets the **endocrine disruptor** criteria for humans for the T-modality. Metribuzin was considered not to meet the ED criteria for EAS-modalities for humans and non-target organisms. Regarding the T-modality, a conclusion on whether the criteria are met or not could not be drawn for non-target organisms (issue not finalised).

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Background

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

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

In accordance with Article 1 of the Regulation, the RMS Estonia and co-RMS Germany received an application from Task Force Metribuzin (consisting of Bayer AG and ADAMA Agan Ltd.) for the renewal of approval of the active substance metribuzin. In addition, Task Force Metribuzin submitted an application to amend an existing residue definition. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Germany), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on metribuzin in the RAR, which was received by EFSA on 30 September 2019 (Estonia, 2019). Furthermore, this conclusion also addresses the assessment of an application to amend an existing residue definition.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicants, Bayer AG and ADAMA Agan Ltd., for consultation and comments on 20 November 2019. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 23 January 2020. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicants were invited to respond to the comments in column 3 of the reporting table. The comments and the applicants' 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 applicants in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 6 April 2020. On the basis of the comments received, the applicants' response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicants, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology.

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 Experts' Teleconference TC 40 and TC 43 (January–February 2021), 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

[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.

Commission Regulation (EU) 2018/605[4], and/or documentary evidence demonstrating that metribuzin may be used such that exposure is negligible, or the conditions for the application of the derogation under Art. 4(7) of Regulation (EC) No 1107/2009 are met.

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

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation 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 and on application to amend existing residue definition took place with Member States via a written procedure in June–July 2023.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative use of metribuzin as a herbicide potato and soybean (field use), as proposed by the applicants. 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, if any, are presented in the conclusion.

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 metribuzin 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 reporting table (1 October 2020);
- the evaluation table (4 July 2023);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft Art 4(7) scientific report;
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Estonia, 2023), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

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

The active substance and the formulation for the representative uses

Metribuzin is the ISO common name for 4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one (IUPAC).

The representative formulated product for the evaluation was 'Sencor SC 600 (Metribuzin SC 600)', a suspension concentrate (SC) containing 600 g/L metribuzin.

The representative uses evaluated were spray application on potato and soybean to control weeds. Full details of the good agricultural practice (GAPs) can be found in the list of end points in Appendix B.

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

[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.

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).

RMS proposed to keep the current individual reference specifications for both ADAMA and Bayer and a minimum purity of 930 g/kg applicable to both. It is noted that the proposed minimum purity for the renewal (930 g/kg) is higher than the minimum purity (910 g/kg) listed in Regulation (EU) 540/2011. Recent batches from industrial scale production were considered for the proposed Bayer reference specification, while the proposed ADAMA reference specification was concluded from the data submitted for the first approval (data gap, see Section 10). Five industrial scale batch data were provided for another source assessed by RMS as equivalent to the current reference specifications of Bayer and ADAMA. The batches used in the toxicological assessment support the current reference specifications (see Section 2). The batches used in the ecotoxicity tests are considered compliant to the current reference specifications (see Section 5). The manufactured technical materials meet the requirements for the minimum purity of 930 g/kg of the existing FAO specification (old procedure, 283/TC/S/F, 1991).

The main data regarding the identity of metribuzin and its physical and chemical properties are given in Appendix B.

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 material and the representative formulation and for the determination of the respective impurities in the technical material.

The components of the residue definition in food/feed of plant origin (metribuzin or DADK-metribuzin) can be monitored by a validated multiresidue quick, easy, cheap, effective and safe (QuEChERs) liquid chromatography with tandem mass spectrometric (HPLC–MS/MS) method in all commodity groups with a limit of quantification (LOQ) of 0.01 mg/kg per analyte, expressed as metribuzin. Efficiency of the extraction procedures used in the method for dry and high acid content commodities was not verified because of lack of metabolism study in these commodities (not required considering the representative uses).

Metribuzin residue in food of animal origin can be determined by HPLC–MS/MS with an LOQ of 0.01 mg/kg in all animal matrices. Efficiency of the extraction procedure used in the method was not verified, as residues in the animal matrices above LOQ, as a result of the representative uses, are not expected.

Metribuzin residue in soil and water can be monitored by HPLC–MS/MS with LOQs of 0.002 mg/kg and 0.05 μg/L, respectively. Appropriate HPLC-UV and HPLC- MS/MS methods exist for monitoring of metribuzin residue in air with LOQ of 1.5 and 1 $\mu g/m^3$, respectively. However, a lower AOEL was derived during the renewal procedure (see Section 2), the available monitoring methods are not sufficiently sensitive to monitor the respective concentration in air according to SANCO/825/00 rev. 8.1; therefore, a data gap for more sensitive monitoring method was set (see Section 10).

HPLC–MS/MS method can be used for monitoring of metribuzin residue in body fluids (plasma) with an LOQ 0.05 mg/L. Metribuzin residue in body tissues can be determined by using the monitoring methods for residue in food of animal origin.

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.

The toxicological profile of the active substance metribuzin and its metabolites was discussed at the Pesticides Peer Review Experts' Teleconference 40 (25–28 January 2021).

Regarding the proposed reference specification, no toxicologically relevant impurities are identified. The test material used in toxicity studies is fully representative of the original and newly proposed reference specification for the active substance and associated impurities (see Section 1).

The **systemic bioavailability** of metribuzin is estimated to be nearly 100% of the orally administered low dose. Excretion is rapid: the majority of radioactivity is excreted in urine and faeces within 24 h. In the rat, metribuzin is widely **distributed** throughout the body, the highest levels are

reached in liver and kidney, and there is no evidence of **bioaccumulation**. The main **metabolic pathway** involves deamination, hydroxylation at the t-butyl side chain, hydrolytic or aminolytic cleavage of the thioalkyl moiety and conjugation. The metabolic profiles in urine and faeces are essentially the same in the rat. The predominant rat metabolites in the excreta of all dose groups are cystein-DA-metribuzin (M12, 12.9–23.7% of the administered radioactivity), DADK-metribuzin (M03, 5.1–10.3%) and DA-metribuzin (M01, 4.1–9.2%). Based on comparative *in vitro* metabolism, no major metabolic inter-species (mouse, rat, rabbit, dog) differences have been observed and no unique human metabolites have been identified.

The **residue definition** for body fluids and tissues includes only metribuzin.

Metribuzin has a moderate **acute oral toxicity**, low dermal and inhalation toxicity, and no irritating or sensitising properties. Metribuzin also tested negative in an *in vitro* phototoxicity assay.

Short-term oral toxicity studies have been provided for rats and dogs. Rabbits have also been investigated after short-term dermal exposure. Irrespective of the exposure route, the liver and kidney are the main target organs in all three animal species. At higher doses, other systems are affected, namely the thyroid gland in rats and rabbits, and the peripheral blood (red blood cells) in rats and dogs. The lowest short-term no observed adverse effect level (NOAEL) of 1.9 mg/kg body weight (bw) per day was identified for increased activity of uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronyltransferase) in female dogs in a 90-day study.

Based on the available **genotoxicity** data package, metribuzin is unlikely to be genotoxic. Testing for photomutagenicity is not required for metribuzin.

After **long-term exposure**, the main target organs of toxicity are the liver in both mice and rats, and the thyroid gland in rats only. In mice, decreased body weight and body weight gain are the basis for setting the long-term NOAEL at 3.4/3.0 mg/kg bw per day (males/females). The relevant NOAEL in rats is 1.3/1.6 mg/kg bw per day (males/females), based on decreased body weight gain, liver enzyme changes and thyroid follicular cell hyperplasia at a LOAEL of 13.8/17.7 mg/kg bw per day in a 2-year rat study. Notably, at 1.3 mg/kg bw per day, a significant increase in the level of the thyroid hormone (TH) T4 is noted. The RMS expressed the view that this low dose should rather be considered as a LOAEL. Conversely, the peer review concluded that in the absence of concomitant histopathological changes in the thyroid gland, hormonal changes should not be considered adverse *per se*, in accordance with the 2019 ECHA/EFSA ED guidance. Still, the peer review concurred with the RMS that changes in serum T4 levels at the lower dose level represent a potential concern for the developing brain[5] (also see discussion in Section 6) and agreed that this deserves a specific investigation, i.e. a developmental neurotoxicity (DNT) study (see list of other outstanding issues under Section 10).

Metribuzin showed no treatment-related tumours in rats and mice and was concluded unlikely to be carcinogenic in humans.

With regard to **reproductive toxicity** studies, post-implantation loss, lower live birth index and increased number of pups dead at birth were observed at 14.8 mg/kg bw per day, resulting in a reproductive NOAEL of 3.3 mg/kg bw per day. Also the parental NOAEL is 3.3 mg/kg bw per day, based on decreased parental body weight and body weight gain, reduced food/water consumption, increased liver γ-GT and hepatocellular hypertrophy at 14.8 mg/kg bw per day in the multigeneration rat study. Finally, the offspring NOAEL is 3.3 mg/kg bw per day mainly based on postnatal survival index between postnatal day (PND) 4 and PND 21.

With regard to **fetal development**, adverse effects were observed both in rats and rabbits. In the main rat developmental toxicity study, the maternal NOAEL is 3 mg/kg bw per day based on hypoactivity, piloerection, decreased body temperature on gestational day (GD) 5 (2 h post-dose), and decreased food intake and the developmental NOAEL is also 3 mg/kg bw per day based on retardations in ossification (unossified digits). In the main rabbit developmental toxicity study, the maternal NOAEL is 10 mg/kg bw per day based on decreased body weight gain and food intake, and the developmental NOAEL is 10 mg/kg bw per day based on late resorptions, post-implantation losses and presacral vertebrae variation.

With respect to **neurotoxicity**, the acute oral NOAEL is 2 mg/kg bw based on decreased motor and locomotor activity, ptosis, oral staining and reduced body temperature at the next higher dose of 5.2 mg/kg bw. The NOAEL for repeated neurotoxicity is the highest dose tested in this study, equivalent to 62/70 mg/kg bw per day (males/females), since no neurotoxic effects were observed at any dose. The reason for the different outcome of the acute and the repeated neurotoxicity studies is

[5] Refer to experts' consultation 2.3 in the Report of Pesticides Peer Review Experts' TC 40 (EFSA, 2023).

unclear. It may possibly depend on metribuzin kinetic differences related to the administration route (gavage in the acute study vs. dietary in the repeated study).

As regards **immunotoxicity**, specific immunotoxic effects were not evident based on the available acceptable studies that investigated immunotoxicity parameters.

Toxicological reference values (TRVs) have been derived for metribuzin.[6] The acceptable daily intake (**ADI**) is 0.0013 mg/kg bw per day, based on the lowest NOAEL of 1.3 mg/kg bw per day for decreased body weight gain, increased levels of circulating liver enzymes and thyroid follicular cell hyperplasia in a 2-year rat study. This NOAEL is in the same order of magnitude of that of 1.6 mg/kg bw per day derived in another rat long-term study, based on lower body weight gain, lower food and water consumption, slight changes in clinical chemistry (higher AST activity and bilirubin concentrations) and in urine parameters. To also account for the incomplete data set (lack of a DNT study), an overall uncertainty factor (UF) of 1000 was applied instead of the standard UF of 100 covering inter- and intra-species differences. This extra UF of 10 underlies the 10-fold difference between the previous and the newly set ADI.

The acute reference dose (**ARfD**), the acceptable operator exposure level (**AOEL**) and the acute AOEL (**AAOEL**) are 0.002 mg/kg bw, based on the NOAEL of 2 mg/kg bw from the rat acute oral neurotoxicity study. As for the ADI, an increased UF of 1000 was applied to account for the uncertainties deriving from the lack of a DNT study. During the previous peer review of metribuzin in 2006, the same acute neurotoxicity study and NOAEL were selected for the derivation of the ARfD and AOEL. However, since the standard UF of 100 was applied at that time, the resulting toxicological reference values were 0.02 mg/kg bw for both the ARfD and the AOEL. No AAOEL was set in 2006.

Dermal absorption of metribuzin in the product for representative use (Metribuzin SC 600) has been assessed in an *in vitro* study with human skin. Based on the EFSA guidance (EFSA, 2017), the dermal absorption values are 0.31% for the concentrate, 31% for the 1.65 g a.s./L spray dilution and 17% for the 2.70 g a.s./L spray dilution. Very similar dermal absorption values are obtained when using the 2012 EFSA guidance, i.e. 0.3% for the concentrate, 32% for the 1.65 g a.s./L spray dilution and 18% for the 2.70 g a.s./L spray dilution.

On request from EFSA in accordance with Commission Implementing Regulation (EU) No 2018/1659, the applicant did not submit any information to demonstrate that non-dietary exposure to metribuzin in plant protection products under realistic conditions of use is negligible. Therefore, negligible exposure was not calculated by the RMS.

Based on the EFSA guidance (2014), exposure estimates for operators are below the (A)AOEL for all representative uses, with the use of gloves during mixing/loading and application with drift reduction (in addition to standard workwear). It is noted that revised calculations taking into account drift reduction were suggested at the final stage of the peer review (EFSA, 2023). Exposure estimates for bystanders and residents exceed the (A)AOEL (**critical area of concern**), while estimates for workers are below the AOEL (without use of gloves) for all representative uses.

Some toxicological studies and information have been provided and discussed[7] for metribuzin's metabolites found as residues (see also Section 3) and/or in groundwater (see also Section 7, Table 2).

For metabolite DA-metribuzin, the parent's TRVs are applicable. DK-metribuzin, DADK metribuzin and 4-methyl-DADK-metribuzin are found as residues in livestock and/or crops (see Section 3) and are also relevant GW metabolites μg/L exceeding 0.75 μg/L (see Sections 4 and 7; Table 2). 4-methyl-DADK-metribuzin is unlikely to be genotoxic in vivo. Mutagenicity and clastogenicity were negative in vitro for both DK-metribuzin and DADK-metribuzin. However, their aneugenic potential cannot be excluded, since it was not properly investigated (**data gap** and **issue not finalised**; see Section 9.1). For DADK metribuzin, an ADI of 0.0025 mg/kg bw per day could be derived from the rat 28-day oral NOAEL to which an overall UF of 2000 was applied to cover for the incomplete data package including aneugenicity assessment. Insufficient data are instead available on the toxicological profiles of DK-metribuzin and 4-methyl-DADK-metribuzin to allow setting reference values (**data gap** and **issue not finalised**; see Section 9.1). Data gaps for in vitro aneugenicity and general toxicity are also applicable to the residue metabolite's conjugate DK-Metribuzin glucuronide (see **issues not finalised** in Section 9.1).

[6] Refer to experts' consultation 2.10 in the Report of the Pesticides Peer Review Experts' Teleconference 40 in January 2021 (EFSA, 2023).

[7] Refer to experts' consultation 2.9 in the Report of the Pesticides Peer Review Experts' Teleconference 40 in January 2021 (EFSA, 2023).

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.

Metribuzin was discussed at the Pesticides Peer Review Experts' Meeting TC 42 (2–4 February 2021).

3.1. Representative use residues

Metabolism was studied in wheat and maize (cereals/grass crops) upon foliar application and in soybean (pulses and oilseeds) and potato (root crops and tuber) upon soil application. The studies were found valid to depict the metabolism in plants and covering the representative use conditions for potato and soybean. Metribuzin is extensively metabolised and only recovered in the food commodities wheat grain and potatoes, but not in soybean seeds and maize kernels. Apart from some metabolites occurring in minor quantities, DA-metribuzin (M1), DK-metribuzin (M2) and DADK-metribuzin (M3) are the major residues. Whereas DA-metribuzin is not occurring in high quantities, DK-metribuzin is major in potato (29% total radioactive residue (TRR)) and its N-glucoside in soybean seeds (11% TRR). DADK-metribuzin was relevant in soybean seeds, both free (35% TRR) and conjugated (16% TRR). Several supporting studies with grapes, tomato, soybean and potato proved evidence of translocation and conjugation of metribuzin in various plant parts.

In order to study the uptake of metribuzin and its soil metabolites, DA-, DK-, DADK- and 4-methyl-DADK-metribuzin, an underdosed rotational crop study with respect to the representative use on potato was performed with wheat (small cereal), kale (leafy crop) and red beet (root/tuber crop) covering all three plant back intervals. In general, the same metabolic pattern as in primary crops was observed with DADK-metribuzin being the major residue except for beet roots. On the basis of these findings, the **plant residue definition for risk assessment (primary and rotational crops)** is proposed as (1) metribuzin, (2) DK-metribuzin and (3) DADK-metribuzin including its conjugates. All three components are to be considered separately to account for different toxicological profiles. However, this proposal is provisional as for DK-metribuzin further toxicological information is needed to confirm its inclusion in the residue definition for risk assessment and for DADK-metribuzin to complete the genotoxicity assessment (see data gap Section 2 for toxicological profile).

Residue field trials were presented with potato and soybeans. However, none of the soybean trials was performed at the critical GAP with application at BBCH 08 but as pre-emergence application (data gap). For potato, results from four trials can be considered for the assessment but as none of them was analysing for conjugates this results in a data gap for sufficient number of residue field trials.

Rotational crop field trials are available for NEU and SEU with carrot, lettuce and barley or wheat. Metribuzin, DA-metribuzin, DK-metribuzin and DADK-metribuzin were below the LOQ of 0.01 mg/kg for all crops at both PBIs in these underdosed trials. As the analytical method used was not employing a hydrolysis step to capture the conjugates, a **data gap** is set for a sufficient number of rotational crop residue trial in NEU and SEU covering the PECsoil for the soil metabolites, analysing all compounds of the residue definitions with a valid analytical method which captures also the conjugated forms and covered by storage stability data. The **plant residue definition for enforcement** is proposed as either metribuzin or DADK-metribuzin. Given that metribuzin is not recovered in soybean seeds and maize dry kernels in the metabolism studies and was not found in the potato residue field trials above the LOQ of 0.01 mg/kg, DADK-metribuzin would be a better marker for the representative uses as it was recovered above the LOQ in all matrices of the metabolism studies and in two of the four valid potato residue field trials.

However, for the final decision risk managers and the MRL review process under Article 12 should take into account the results from residue trials of all authorised uses. Metribuzin and DADK-Metribuzin are stable under standard processing hydrolysis conditions. Processing factors were not established but might be needed depending on the outcome of the residue field trials with potato and soybean (see data gap above).

For the representative uses on potatoes and soybean, stability for metribuzin and DK-metribuzin of 24 months could be agreed on basis of a recent storage stability study (2015). However, pending toxicity assessment of DK-metribuzin, this will need to be confirmed by additional data to investigate the potential degradation of DK to form DADK during the storage as indicated by a former study (1999).[8]

[8] Refer to to experts' consultation 3.1 in the Report of Pesticides Peer Review Experts' TC 42 (EFSA, 2023).

Metabolism studies with goat and poultry are available and indicate that the metabolic picture in animals is similar to plants but more conjugation takes place. In goats, two additional metabolites were identified as major. Buthylthione-metribuzin (M10) in fat (37% TRR) and muscle (20% TRR) and sulfamate metribuzin (M15) in milk (84% TRR) and kidney (40% TRR). As the metabolism study is highly overdosed, a transfer of these two metabolites to animal commodities is not likely for the currently proposed uses. On this basis, the **animal residue definition for risk assessment** is proposed as: (1) Metribuzin (free and conjugated) and DA-metribuzin (M1), expressed as parent, (2) DK-metribuzin (M2) plus conjugates and (3) DADK-metribuzin (M3) plus conjugates. This proposal is provisional as for DK-metribuzin (M2) further toxicological information is needed to confirm its inclusion in the residue definition for risk assessment and for DADK-metribuzin to complete the genotoxicity assessment (see data gap in Section 2). As metribuzin is recovered in all animal matrices it is proposed as **residue definition for enforcement**. Feeding studies which are not guideline and GLP compliant with poultry and ruminants are available but not acceptable for risk assessment due to several shortcomings. In case new feeding studies would be required to derive and propose MRLs, either due to updated dietary burden calculation according to the new plant risk assessment residue definition and/or due to additional uses, particular attention should be given to the following points: The study would need to be conducted with realistic dosing rates with respect to the proposed but also possible future uses and quantifying also metabolites M15 and M10 to assess their quantitative relevance for potential inclusion in the risk assessment residue definition. It is noted that if hydrolysis steps are performed in the analytical method of the study, it should be considered that M15 is hydrolysed and quantified together with metribuzin. As no data were submitted, a data gap is set to provide data or information on residue levels in pollen and in bee products for human consumption resulting from residues taken up by honeybees from intended use on soybean at blossom (see Section 10). The consumer risk assessment and the dietary burden calculation are not finalised due to data gaps related (1) to the toxicological profile of DK-metribuzin (data gap, see Section 2) and (2) residue field trials for all representative uses (data gap, see above). However, it should be noted that when considering the new toxicological reference values for metribuzin and only the residues from the four valid residue field trials with potato (all below LOQ of 0.01 mg/kg) the acute risk calculated with PRIMo 3.2 is already 77% of the ARfD (potato, UK infant). For the groundwater metabolite DADK-metribuzin, the additional contribution to the consumer intakes through drinking water ranged from 17% of the ADI for adults to 75% of the ADI for infants. The assessment is provisional as data for genotoxicity are outstanding (data gap, see Section 2). For the other two groundwater metabolites, DK-metribuzin and 4-methyl-DADK-metribuzin, the assessment is not possible as no ADIs were available to perform this calculation.

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

3.2. Maximum residue levels

The requests to increase MRLs for potato and soybean were supported by residue field trials. As not all of the trials are valid (see Section 3.1), the proposal cannot be supported.

A further MRL application was received to change the current residue definition for enforcement (metribuzin) to 'sum of metribuzin, DA-metribuzin, DK-metribuzin, DADK-metribuzin, expressed as metribuzin'. This proposal is not supported due to the fact that DADK-metribuzin has a different toxicological profile then the parent compound and for DK-metribuzin the toxicological profile could not be established (data gap, see Section 3.1). For further details, please refer to the Report of Pesticides Peer Review Experts' Meeting TC 42.

4. Environmental fate and behaviour

Metribuzin was discussed at the Pesticides Peer Review Experts' Meeting TC 42 (26–27 January 2021).

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, metribuzin exhibited low persistence, forming the major (>10% applied radioactivity (AR)) metabolites DA-metribuzin (max. 5% AR) which exhibited low persistence, DK-metribuzin (max. 14% AR) and DADK-metribuzin (max. 14% AR), which exhibited low to moderate persistence, and

metabolite 4-methyl-DADK-metribuzin (max. 5% AR), which exhibited moderate to medium persistence. Mineralisation of the 5-^{14}C radiolabel to carbon dioxide accounted for 21–33% AR after 63 days. The formation of unextractable residues (not extracted by acetonitrile/water) for this radiolabel accounted for 41–52% AR after 63 days. Satisfactory anaerobic soil degradation and soil photolysis studies on metribuzin were not available (**data gaps, see Section 10**).

Metribuzin exhibited very high to high mobility in soil. It was concluded that the adsorption of metribuzin was not pH dependent. Metabolite DA-metribuzin exhibited very high to high soil mobility and metabolite 4-methyl-DADK-metribuzin exhibited very high soil mobility. It was concluded that adsorption of DA-metribuzin is pH dependent with adsorption decreasing in alkaline soils. For metabolites DK-metribuzin and DADK-metribuzin, reliable batch adsorption studies in soil were not available (**see Section 9.1**).

In a lysimeter study of 2-year duration dosed at 500 g/ha/year cropped with potatoes followed by winter wheat and winter barley all chromatographically resolved components in leachate accounted for < 0.01 μg/L, as annual average concentrations, except for DADK-metribuzin which amounted for 0.14–0.23 μg/L. A new metabolite desmethylthio-metribuzin was found in the leachate with annual average concentrations of 0.09–0.1 μg/L.

In laboratory incubations in dark aerobic natural sediment water systems, metribuzin exhibited moderate to medium persistence, forming the major metabolites DA-metribuzin (max. 22% AR in water and max 22% in sediment), DK-metribuzin and DADK-metribuzin (max 12.7% AR in total system as sum of DK-metribuzin and DADK-metribuzin). The unextractable sediment fraction (not extracted by acetonitrile/water) was the major sink for the ^{14}C radiolabel, accounting for 22–38% AR at study end (100 days) and for the 6-^{14}C radiolabel, accounting for 23–28% AR at study end (200 days). Mineralisation of these radiolabels accounted for 2.1–3.5% AR and 1.8% AR at the end of the study, respectively. The rate of decline of metribuzin in a laboratory sterile aqueous photolysis experiment was fast relative to that occurred in the aerobic sediment water incubations. No chromatographically resolved component (excluding metribuzin and DA-metribuzin (max. 84% AR)) accounted for >10% AR.

The necessary surface water and sediment exposure assessments (predicted environmental concentrations (PEC) calculations) were carried out for the metabolites DA-metribuzin, DK-metribuzin, DADK-metribuzin and 4-methyl-DADK-metribuzin, using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator). For the active substance metribuzin and metabolites, appropriate step 3 (FOCUS, 2001) and step 4 calculations were available. The step 4 calculations appropriately followed the FOCUS (FOCUS, 2007) guidance, with no-spray drift buffer zones of up to 20 m being implemented for the drainage scenarios (representing a 72–93% spray drift reduction), and combined no-spray buffer zones with vegetative buffer strips of up to 20 m (reducing solute flux in run-off by 80% and erosion run-off of mass adsorbed to soil by 95%) being implemented for the run-off scenarios. The SWAN tool (version 5.0.1) was appropriately used to implement these mitigation measures in the simulations. However, risk managers and others may wish to note that while run-off mitigation is included in the step 4 calculations available, the FOCUS (FOCUS, 2007) report acknowledges that for substances with K_{Foc} < 2000 mL/g (i.e. metribuzin), the general applicability and effectiveness of run-off mitigation measures had been less clearly demonstrated in the available scientific literature, than for more strongly adsorbed compounds.

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[9] for metribuzin and its metabolites. The potential for groundwater exposure from the representative uses by metribuzin and metabolites DA-metribuzin and desmethylthio-metribuzin above the parametric drinking water limit of 0.1 μg/L was concluded to be low in geoclimatic situations that are represented by all nine FOCUS groundwater scenarios.

For the representative use on potato, the 80th percentile annual average concentrations leaving the top 1 m soil layer were estimated to be > 0.1 μg/L at seven out of nine scenarios for metabolite DK-metribuzin, and at all scenarios for metabolites DADK-metribuzin and 4-methyl-DADK-metribuzin.

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

For the representative use on soybean (at higher application rate), the 80th percentile annual average concentrations leaving the top 1 m soil layer were estimated to be > 0.1 μg/L at one out of one scenario for metabolites DK-metribuzin, DADK-metribuzin and 4-methyl-DADK-metribuzin.

For the representative use on soybean (at lower application rate), the 80th percentile annual average concentrations leaving the top 1 m soil layer were estimated to be > 0.1 μg/L at one out of one scenario for metabolites DADK-metribuzin and 4-methyl-DADK-metribuzin, and < 0.1 μg/L at one out of one scenario for metabolite DK-metribuzin.

It should be noted that concentrations in groundwater were >0.75 μg/L for metabolite DK-metribuzin (representative use on potato), DADK-metribuzin (representative use on potato) and 4-methyl-DADK-metribuzin (representative use on potato). This results in an assessment that could not be finalised (see Section 9.1).

The applicant did not provide appropriate information to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater is abstracted for the production of drinking water. This results in an assessment that could not be 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 (2002), SETAC (2001), EFSA (2009, 2013) and EFSA PPR Panel (2013).

The batches used in the ecotoxicological toxicity tests are considered compliant to the current reference technical specifications (see Section 1).

Some aspects of the risk assessment of metribuzin were discussed at the Pesticides Peer Review Experts' Meeting TC 43 (1–5 February 2021).

Based on the available acute and long-term data and risk assessment, low risk (both acute and reproductive) to **birds**[10] and **mammals**[11] for all relevant[12] routes of exposure and all representative uses was concluded.

Low risk to birds and mammals was concluded from exposure to pertinent plant metabolites DA-metribuzin, DK-metribuzin and DADK-metribuzin. It has to be noted that a risk assessment from exposure to metabolites was only presented for mammals. However, when considering the outcome of the avian risk assessment for metribuzin and the lower level of exposure that is expected for metabolites, low risk to birds was also concluded.

Acute and chronic toxicity data were available for **fish** and **aquatic invertebrates** with metribuzin. Chronic toxicity data with **algae** (both green algae and diatoms) and **aquatic macrophytes** (both *Lemna* and *Myriophyllum* sp.) were available with metribuzin and the representative formulation.

Based on the available data and Tier 1 risk assessment, low risk to fish and aquatic invertebrates was concluded using up to FOCUS Step 3 PEC surface water estimations for all representative uses. Low risk was concluded when implementing risk mitigation measures up to 20 m (m) vegetative buffer strip and 20 m no-spray buffer zone for four out of six (i.e. D3, D4, R1 and R2) FOCUS scenarios for the representative uses in potato for algae and plants. For the representative uses on soybean, low risk to algae and aquatic macrophytes represented by *Myriophyllum* sp. was concluded when implementing risk mitigation measures up to 20 m vegetative buffer strip and 20 m no-spray buffer zone for all relevant scenarios. The implementation of mitigation measures was, however, not sufficient to conclude low risk for one out of two (R3) FOCUS scenarios for aquatic macrophytes represented by *Lemna* sp.

The experts at the Pesticides Peer Review Experts' Meeting TC 43 discussed the suitability of available refinement options[13] including refined exposure studies[14] with *Lemna*. Overall, when using the refined exposure studies, low risk to *Lemna* sp. was concluded for situations represented by the scenario R3 for the representative uses on soybean and FOCUS Step 3 PECsw (lower application rate) and for situation represented by the FOCUS scenario R3 for the representative uses on potato and

[10] See experts' consultation point 5.2 in the Report of the Pesticides Peer Review Experts' TC 43 (EFSA, 2023).
[11] See experts' consultation point 5.1 in the Report of the Pesticides Peer Review Experts' TC 43 (EFSA, 2023).
[12] Based on the log Kow, a risk assessment from secondary poisoning was triggered neither for metribuzin nor any of the pertinent metabolites.
[13] See experts' consultation point 5.4 in the Report of the Pesticides Peer Review Experts' TC 43 (EFSA, 2023).
[14] See experts' consultation point 5.3 in the Report of the Pesticides Peer Review Experts' TC 43 (EFSA, 2023).

soybean (high application rate) with the implementation of mitigation measures up to 20 m vegetative buffer strip and 20 m no-spray buffer zone.

For the pertinent surface water metabolites, DA-metribuzin and DADK-metribuzin, acute toxicity data with fish and aquatic invertebrates were available together with algae and aquatic macrophytes toxicity data. Chronic toxicity data with the metabolite DADK-metribuzin were also available with fish and aquatic invertebrates. The metabolite DK-metribuzin and 4-methyl-DADK-metribuzin were only tested with algae and aquatic plants which were the most sensitive groups. Low risk to all pertinent metabolites for all representative uses was concluded.

For **honeybees**, acute (oral and contact), chronic and repeated exposure larval studies were available either with both metribuzin and the representative formulation or only with one of the two. In addition, a brood development study according to Oomen et al. (1992) and two semi-field studies according to OECD 75 were available. Acute toxicity studies (oral and contact) with bumblebees were also available with metribuzin. However, no risk assessment was submitted for this group of bees.

Based on the available data and Tier 1 risk assessment according to EC (2002), low acute risk to honeybees was concluded for all the representative uses. No Tier 1 risk assessment according to EFSA (2013) was available. The available higher tier studies were discussed at the Pesticides Peer Review Experts' Meeting TC 43.[15] Overall, although the available higher tier studies were conducted in worst-case conditions compared to the representative uses for metribuzin, adverse effects on brood were observed and the available weight of evidence did not allow to conclude low risk to honeybees (mainly chronic and to larvae) for all representative uses (critical area of concern, see Section 9.2).

No information on accumulative effects and no toxicity data on solitary bees were available. No information was available to address the risk to honeybees when exposed to pertinent metabolites formed in pollen and nectar (data gap, see Section 10).

Tier 1 studies and Tier 2 toxicity studies were available for the two standard **non-target arthropod species** and two additional species. Based on the available data and risk assessment, low risk was concluded for the representative use on soybean. High in-field risk was concluded for the representative uses in potato. Low off-field risk was concluded for all representative uses. Available refinements were discussed at the Peer Review Experts' meeting TC 43,[16] i.e. residue decline studies on leaves and an aged residue study with *T. pyri*.

The residue decline studies were not considered reliable, and therefore, the DT50 in leaves could not be refined. Moreover, the aged residue study was conducted at a lower application rate than the representative uses on potato. Therefore, overall, a high risk to non-target arthropods was concluded for the representative uses in potato.

Earthworms, **soil macro-organisms** and **soil microorganisms** were tested with the representative formulation and the pertinent soil metabolites DA-metribuzin, DK-metribuzin, DADK-metribuzin and Metribuzin-4-methyl-DADK. Based on the available data, low risk was concluded for all representative uses of metribuzin and its pertinent soil metabolites.

For **non-target terrestrial plants**, based on the available toxicity data and Tier 2 risk assessment,[17] low risk was concluded when mitigation measures are comparable to 5 m non-spray buffer zone or 1 m no-spray buffer zone and 50% drift reduction (representative uses in potato and soybean use at the high application rate) and 1 m no-spray buffer zone for the representative use on soybean at the low application rate.

Low risk to organisms involved in the **biological methods for sewage treatment** was concluded for all representative uses.

6. Endocrine disruption properties

With regard to the assessment of the endocrine disruption (ED) potential of metribuzin **for humans** according to the ECHA/EFSA guidance (2018), in determining whether metribuzin 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 therefore provides a weight-of-evidence analysis of the potential interaction of metribuzin with the EAS and T signalling pathways using the available evidence in the data set.

[15] See experts' consultation point 5.6 of the Peer Review Experts' consultation TC 43 (EFSA, 2023).
[16] See experts' consultation point 5.5 of the Peer Review Experts' consultation TC 43 (EFSA, 2023).
[17] See experts' consultation point 5.7 of the Peer Review Experts' consultation TC 43 (EFSA, 2023).

The **T-modality** was 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)) were observed in studies of different duration and/or in different species.

In addition, a comparative thyroid assay (CTA) study confirmed the concern that metribuzin is perturbing the hypothalamic–pituitary–thyroid (HPT) axis with changes in THs and TSH. In this study, metribuzin-induced effects on thyroid hormones in GD 20 foetuses were in the same range of those observed with the positive control 6-N-Propyl-2-Thiouracil (PTU).

A pattern of hormonal changes characterised by an increase in T4 level in pups at PND 4 and 21 followed by an increase in TSH at high doses in pups at PND 4 was observed in the CTA study. The adversity reported in the CTA study was based on the overall perturbation of HPT axis as it is known that both decreases as well as increases in thyroid hormones are of concern for the developing brain.

Perturbation of the HPT axis was also observed across the metribuzin data set, with a combination of changes in T4, TSH and/or thyroid histopathology. They were reported to occur in the 28-day studies in rats, in a 9-week mechanistic study in rats, 21-day pubertal study in rat and in a developmental toxicity study in rats. An increase in T4 was also observed in the 2-year rat study and in the dermal toxicity study in rabbits.

The postulated mode of action (MOA) indicated CAR/PXR induction as the plausible molecular initiating event (MIE) and phase I/II enzymes induction as the plausible key events (KE); however, the plausible MIE was not experimentally investigated and the available ToxCast data[18] did not support the above hypothesis. The new in vitro comparative UGT assay does not provide sufficient evidence to conclude on the human relevance of the mode of action (MoA). Several uncertainties and limitations in the in vitro comparative study were identified. Moreover, the available information on endocrine activity, including information on molecular initiating events (MIEs) i.e. TPO, NIS, CAR/PXR, DIO inhibition, are not sufficient to conclude on the MoA for metribuzin. Phase II enzyme induction is a plausible MoA at high doses in the rat; however, this is not considered sufficient to explain changes in T4 at low doses possibly occurring as consequence of different MoA.

In the studies conducted with metribuzin, the lowest observed adverse effect level (LOAEL), where T- mediated adversity was observed in males at 1-year interim sacrifice and at termination in the form of thyroid histopathology (thyroid follicular cell hyperplasia), is 13.8 mg/kg bw per day from a 2-year toxicity study in rats. A no observed adverse effect level (NOAEL) of 1.3 mg/kg bw per day can be derived for thyroid histopathology.

It was noted that changes in thyroid hormones, i.e. increases in T4, were observed in studies of different duration and at doses below the LOAEL derived for thyroid histopathology. Although these changes were indicative of a perturbation of the HPT axis, the lack of a corresponding thyroid histopathology characterisation prevent their use for the definition of a NOAEL.

Based on the available and sufficient dataset and the mode of action (MoA) analysis, it was concluded that the ED criteria for T-modality are met for metribuzin (**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 reported above for humans also applies to **wild mammals as non-target organisms for EAS-modalities**. The T-mediated adverse effects observed in mammals are not considered to be relevant for wild mammal populations, and therefore, the outcome of the assessment reported above for humans does not apply to wild mammals as non-target organisms regarding the T-modality.

For non-target organisms other than mammals, no studies investigating T-endocrine activity or T-mediated endocrine adversity were available. Therefore, overall a conclusion could not be drawn. For the EAS-modalities, a fish short-term reproduction assay was available and, although it showed some deficiencies, it did not show a pattern of EAS-endocrine activity.

According to point 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that metribuzin meets the ED criteria for humans for the T-modality (data gap and critical area of concern, see Section 9.1). Metribuzin was considered not to meet the ED criteria for EAS-modalities for humans and non-target organisms.

[18] https://comptox.epa.gov/dashboard/chemical/invitrodb/DTXSID6024204 [accessed on 4/05/2023].

Regarding the T-modality, a conclusion on whether the criteria are met or not could not be drawn for non-target organisms (data gap and issue not finalised, see Section 9.1).

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

Table 1: Soil

Compound (name and/or code)	Ecotoxicology
Metribuzin	Low risk
DA-metribuzin	Low risk
DK-metribuzin	Low risk
DADK-metribuzin	Low risk
4-methyl-DADK-metribuzin	Low risk

Table 2: Groundwater[(a)]

Compound (name and/or code)	> **0.1 µg/L at 1 m depth for the representative uses[(b)] Step 2**	**Biological (pesticidal) activity/ relevance Step 3a.**	**Hazard identified Steps 3b. and 3c.**	**Consumer RA triggered Steps 4 and 5**	**Human health relevance**
Metribuzin	No	Yes	–	No	Yes
DA-metribuzin (M01)	No	Not triggered	Not triggered LD_{50}: 468 mg/kg bw (rat) Covered by the parent TRVs	No	Not triggered
DK-metribuzin (M02)	Yes Potato: 7/9 FOCUS scenarios (0.27–**2.33** µg/L) Soybean (higher application rate): 1/1 FOCUS scenarios (0.12 µg/L) Soybean (lower application rate): No	No	Open Genotoxicity – Unlikely to be mutagenic or clastogenic. – **Aneugenicity not properly investigated** (data gap) General toxicity – LD_{50}: 266 mg/kg bw (rat) – Insufficient data to derive an ADI	Yes, but inconclusive as no TRV is set	Open
DADK-metribuzin (M03)	Yes Potato: 9/9 FOCUS scenarios (0.4–**12.5** µg/L) Soybean (higher application rate): 1/1 FOCUS scenarios (0.8 µg/L) Soybean (lower application rate): 1/1 FOCUS scenarios (0.5 µg/L)	No	Open Genotoxicity – Unlikely to be mutagenic or clastogenic. – **Aneugenicity not properly investigated** (data gap) General toxicity – LD_{50}: 700 mg/kg bw (rat) – ADI: 0.0025 mg/kg bw per	Yes, but provisional due to outstanding genotoxicity assessment	Open

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
			day (28-day oral rat NOAEL, UF 2000 for incomplete data package including lack of aneugenicity assessment).		
4-methyl-DADK-metribuzin (M17)	Yes Potato: 9/9 FOCUS scenarios (0.6–**5.8** µg/L) Soybean (higher application rate): 1/1 FOCUS scenarios (0.6 µg/L) Soybean (lower application rate): 1/1 FOCUS scenarios (0.4 µg/L)	No	Open Genotoxicity Unlikely to be genotoxic in vivo General toxicity – LD_{50}: 918 mg/kg bw (rat) – Insufficient data to derive an ADI	Yes, but inconclusive as no TRV is set	Open
Desmethylthio-metribuzin (M18)	No	Not triggered	Not triggered Genotoxicity Unlikely to be genotoxic in vivo	No	Not triggered

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

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Metribuzin	Low risk to fish and aquatic invertebrates. High risk for 2/6 FOCUS scenarios for algae and for 1/6 for plants for the representative use on potato. Low risk for the representative uses on soybean.
DA-metribuzin	Low risk
DK-metribuzin	Low risk
DADK-metribuzin	Low risk
4-methyl-DADK-metribuzin	Low risk

Table 4: Air

Compound (name and/or code)	Toxicology
Metribuzin	> 2.045 mg/L air /4 h (*dust; 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.

For aquatic organisms and non-target terrestrial plants, risk mitigation measures were needed to conclude low risk as indicated below (Table 5).

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

Representative use	Potato N-EU	Potato C-EU	Potato S-EU	Soybean C-EU (330 g a.s./ha)	Soybean S-EU (210 g a.s./ha)
	Spraying	Spraying	Spraying	Spraying	Spraying Spraying
Operator risk	Use of PPE is required	Use of PPE is required	Use of PPE is required	Use of PPE is required	Use of PPE is required
Worker exposure					
Bystander/ resident exposure	Exposure estimates exceed the (A)AOEL	Exposure estimates exceed the (A)AOEL	Exposure estimates exceed the (A)AOEL	Exposure estimates exceed the (A)AOEL	Exposure estimates exceed the (A)AOEL
Risk to aquatic organisms	RMM equivalent to 20 m no-spray buffer zone and 20 m vegetative buffer strip for 5/6 FOCUS scenario (D3, D4, R1, R2 and R3)	RMM equivalent to 20 m no-spray buffer zone and 20 m vegetative buffer strip for 4/6 FOCUS scenario (D3, D4, R1, R2 and R3)	RMM equivalent to 20 m no-spray buffer zone and 20 m vegetative buffer strip for 4/6 FOCUS scenario (D3, D4, R1, R2 and R3)	RMM equivalent to 20 m no-spray buffer zone and 20 m vegetative buffer strip for 1/2 FOCUS scenario (R3)	RMM equivalent to 20 m no-spray buffer zone and 20 m vegetative buffer strip for 1/2 FOCUS scenario (R3)
Non-target terrestrial plants	RMM comparable to either 5 m non-spray or 1 m and 50% drift reduction	RMM comparable to either 5 m non-spray or 1 m and 50% drift reduction	RMM comparable to 5 m non-spray or 1 m and 50% drift reduction	RMM comparable to either 5 m non-spray buffer zone or 1 m no-spray buffer zone and 50% drift reduction	RMM comparable to 1 m no-spray buffer zone

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[19] 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.

[19] 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.

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

1) The assessment of the endocrine-disrupting properties for non-target organisms.
    a) Further data would be needed to conclude on whether the criteria as laid down in point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 are met, i.e. a test according to OECD TG 231.[20]
2) The consumer dietary risk assessment could not be concluded since the risk assessment residue definition for plants and animals could not be finalised, and the livestock exposure assessment cannot be conducted (see Sections 3.1 and 3.2).
    a) The toxicological profile of DK-metribuzin (M2) and its glucuronide-conjugate should be addressed to confirm its inclusion in the residue definition for risk assessment (relevant for all uses evaluated, see Sections 2, 3.1 and 3.2).
    b) The genotoxic profile of DADK-metribuzin (M3) should be addressed (relevant for all uses evaluated, see Sections 2, 3.1 and 3.2).
    c) A sufficient number of residue field trails with soybean for each zone conducted according to the critical GAP, analysing for all compounds covered by the residue definition with a valid analytical method and covered by storage stability data (relevant for use on soybean, see Sections 3.1 and 3.2).
    d) A sufficient number of residue field trails with potato for each zone conducted according to the critical GAP, analysing for all compounds covered by the residue definition with a valid analytical method and covered by storage stability data (relevant for use on potato, see Sections 3.1 and 3.2).
    e) A sufficient number of rotational crop residue trial in NEU and SEU covering the PECsoil for the soil metabolites, analysing all compounds of the residue definitions with a valid analytical method which captures also the conjugated forms and covered by storage stability data
3) The hazard identification and additional contribution of the groundwater metabolites 4-methyl-DADK-metribuzin, DADK-metribuzin and DK-metribuzin to the consumer intakes through drinking water cannot be assessed, and consequently, their groundwater relevance was not concluded
    a) The toxicological profile of 4-methyl-DADK-metribuzin should be addressed to derive an ADI (relevant for all uses evaluated, see Sections 2, 3.1, 3.2 and 4).
    b) For DK-metribuzin (M02) see 2.a
    c) For DADK-metribuzin (M03) see 2.b
    d) Reliable data on the adsorption/desorption of metabolites DK-metribuzin and DADK-metribuzin in soil were not available (relevant for all representative uses evaluated; see Section 4).
4) The consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water (see Sections 3 and 4)
    a) Satisfactory information was not available to demonstrate that residues that may originate from metribuzin 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 and groundwater abstracted for the production of drinking water (relevant to comply with the conditions of approval, not dependent of any specific use, see Section 4).

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

[20] A level 3 test is needed to sufficiently investigate the endocrine activity. However, if that is positive, further data would be needed to investigate adversity, i.e. a test according to OECD TG 241.

(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

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

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

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

5) Bystander and resident exposure estimates exceed the A(AOEL) value (relevant for all representative uses evaluated; see Section 2).
6) The available higher tier studies for bees were not sufficient to exclude high risk to bees (relevant for all the representative uses; see Section 5).
7) Metribuzin meets the ED criteria for the T-modality for humans as laid down in 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).

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

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 6.)

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

Representative use		**Potato**	**Soybean**
		Spraying	**Spraying**
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Resident/bystander risk	Risk identified	X[5]	X[5]
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[2,3,4]	X[2,3,4]
Risk to wild non-target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[6]	X[6]
	Assessment not finalised		
Risk to aquatic organisms	Risk identified	X (High risk for 2/6 FOCUS scenarios for algae and for 1/6 for plants)	
	Assessment not finalised		

Representative use		Potato Spraying	Soybean Spraying
Groundwater exposure to active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached[(a)]		
	Parametric value of 10 µg/L[(b)] breached		
	Assessment not finalised	X[3]	X[3]

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

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

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

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:

- Representative batches from the recent and current (not older than 5 years) industrial scale production for the ADAMA source used to set the reference specification or a justification if such data cannot be provided (relevant for all representative uses evaluated; see Section 1).
- More sensitive monitoring method in air (i.e. LOQ suitable for AOEL of 0.002 mg/kg bw) (relevant for all representative uses evaluated; see Section 1).
- Data on the developmental neurotoxicity (DNT) potential of metribuzin are not available (relevant for all representative uses evaluated; see Section 2).
- Data on residues of metribuzin and its metabolites included in the risk assessment residue definition in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom were not available (relevant for use on soybean, it is acknowledged that no guidance/test guideline was available at the time of submission for addressing this data requirement; see Section 3).
- A soil degradation study on metribuzin long enough to clearly identify the maximum formation of metabolites (relevant for all representative uses evaluated; see Evaluation Table Section 4, data requirement 4.1).
- A valid anaerobic soil degradation study on metribuzin (relevant for all representative uses, see Section 4).
- A valid soil photolysis study on metribuzin (relevant for all representative uses, see Section 4).
- Summaries of two lysimeter studies on metribuzin (relevant for all representative uses evaluated; see Evaluation Table Section 4, data requirement 4.8).
- Further data were not available to address the risk to honeybees via exposure to metabolites formed in pollen and nectar (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
AOEL	acceptable operator exposure level
AR	applied radioactivity
AR	androgen receptor
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
bw	body weight
CFU	colony forming units
DNT	developmental neurotoxicity
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FSTRA	Fish Short-Term Reproduction Assay
GAP	Good Agricultural Practice
HPLC	high-pressure liquid chromatography or high-performance liquid chromatography
HPLC–MS	high-pressure liquid chromatography–mass spectrometry
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
iv	intravenous
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
K_{Foc}	Freundlich organic carbon adsorption coefficient
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
mm	millimetre (also used for mean measured concentrations)
mN	milli-Newton

MOA	mode of action
MRL	maximum residue level
MS	mass spectrometry
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
Pa	pascal
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PPE	personal protective equipment
ppm	parts per million (10^{-6})
QSAR	quantitative structure–activity relationship
r^2	coefficient of determination
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
SC	suspension concentrate
SFO	single first-order
SMILES	simplified molecular-input line-entry system
$t_{1/2}$	half-life (define method of estimation)
TRR	total radioactive residue
TSH	thyroid-stimulating hormone (thyrotropin)
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

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

Properties		Conclusion[(a)]
CMR	Carcinogenicity (C)	Metribuzin is not considered to be carcinogenic, mutagenic or toxic for reproduction.
	Mutagenicity (M)	
	Toxic for Reproduction (R)	
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 metribuzin meets the ED criteria for humans for the T-modality. Metribuzin was considered not to meet the ED criteria for EAS-modalities for humans and non-target organisms. Regarding the T-modality, a conclusion on whether the criteria are met or not could not be drawn for non-target organisms.
POP	**Persistence**	Metribuzin 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**	Metribuzin 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**	Metribuzin is not considered to be a very persistent, very bioaccumulative substance according to point 3.7.3 of Annex II of Regulation (EC) 1107/ 2009.
	Bioaccumulation	

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

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

Appendix B can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8140

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

Appendix C can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8140

Appendix D – Data collection set

Validated Excel files submitted by 13 MS (Austria, Belgium, Bulgaria, Croatia, Estonia, France, Germany, Hungary, Latvia, the Netherlands, Poland, Spain, Sweden) 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 metribuzin as herbicide to control a serious danger to plant health which cannot be contained by other available means.

Appendix D can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8140

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

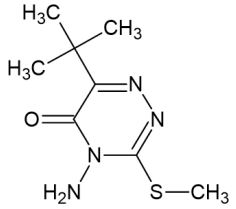
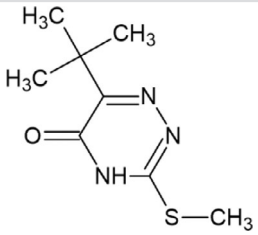
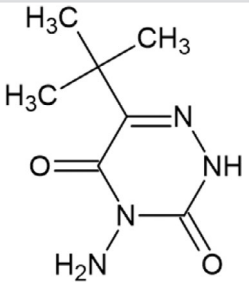
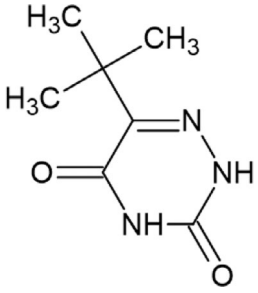
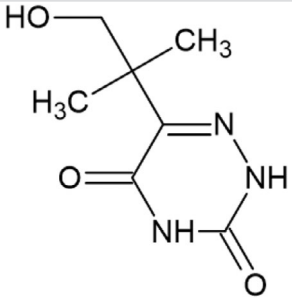
Note these classes and descriptions are unrelated to any persistence class associated with the active substance cut-off criteria in Annex II of Regulation (EC) No 1107/2009. For consideration made in relation to Annex II, see Appendix A.

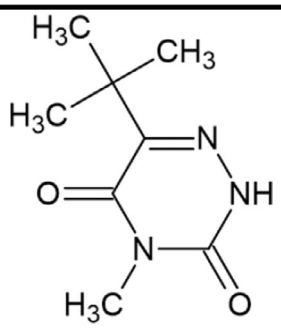
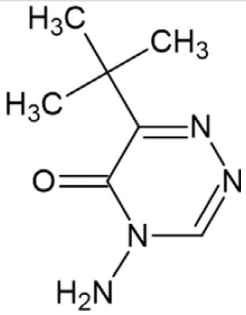
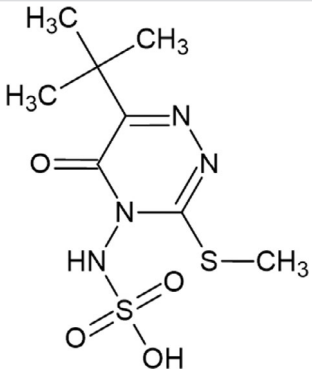
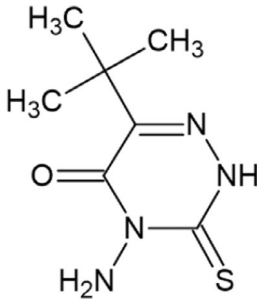
Wording	K_{oc} (either K_{Foc} or K_{doc}) mL/g
Very high mobility	0–50
High mobility	51–150
Medium mobility	151–500
Low mobility	501–2,000
Slight mobility	2,001–5,000
Immobile	> 5,000

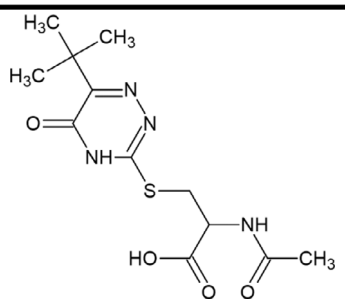
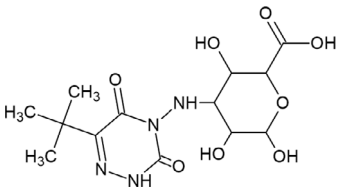
Based on McCall et al. (1980).

[21] 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]
metribuzin, active substance, a.s., BCS-AA51359	4-amino-6-*tert*-butyl-3-(methylthio)-1,2,4-triazin-5(4*H*)-one O=C1C(=NN=C(SC)N1N)C(C)(C)C FOXFZRUHNHCZPX-UHFFFAOYSA-N	
DA-metribuzin, M01, desamino-metribuzin, BCS-AA91084	6-*tert*-butyl-3-(methylsulfanyl)-1,2,4-triazin-5(4*H*)-one CC(C)(C)C1=NN=C(SC)NC1=O MIWRSUQXSCLDNV-UHFFFAOYSA-N	
DK-metribuzin, M02, diketo-metribuzin, BCS-AG59919	4-amino-6-*tert*-butyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione O=C1N(N)C(=O)NN=C1C(C)(C)C AHBXXEZLRFCZSF-UHFFFAOYSA-N	
DADK-metribuzin, M03, desaminodiketo-metribuzin, BCS-AA68848	6-*tert*-butyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione O=C1NC(=O)NN=C1C(C)(C)C ZARIFGFXSIZTAK-UHFFFAOYSA-N	
t-BuOH-DADK-metribuzin, M04, hydroxy-t-butyl-DADK	6-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione OCC(C)(C)C1=NNC(=O)NC1=O KPRRHPBFRZPBBH-UHFFFAOYSA-N	

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
4-methyl-DADK-metribuzin, M17, BCS-AA10228	6-*tert*-butyl-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)-dione O=C1N(C)C(=O)NN=C1C(C)(C)C HAMOEZWHUZLDGI-UHFFFAOYSA-N	
Desmethylthio-metribuzin, M18, U1, BCS-AA10033	4-amino-6-*tert*-butyl-1,2,4-triazin-5(4*H*)-one O=C1C(=NN=CN1N)C(C)(C)C GMHFNNALALGFKT-UHFFFAOYSA-N	
Sulfamate-metribuzin, M15, Sulfamate-conjugate #8, #8a, #8b	[6-*tert*-butyl-3-(methylsulfanyl)-5-oxo-1,2,4-triazin-4(5*H*)-yl]sulfamic acid OS(=O)(=O)NN1C(=NN=C(C1=O)C(C)(C)C)SC CFTYOBVLLJEBCM-UHFFFAOYSA-N	
Butylthione-metribuzin, M10, BCS-AA66387	4-amino-6-*tert*-butyl-3-sulfanylidene-3,4-dihydro-1,2,4-triazin-5(2*H*)-one O=C1N(N)C(=S)NN=C1C(C)(C)C OFKAVNQBCRJBJE-UHFFFAOYSA-N	 Other tautomeric forms are possible (condition dependent)

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[c]
Cystein-DA-metribuzin, M12, Cystein-DA, DA-N-Ac-Cys	*N*-acetyl-*S*-(6-*tert*-butyl-5-oxo-4,5-dihydro-1,2,4-triazin-3-yl)cysteine CC(C)(C)C1=NN=C(SCC(NC(C)=O)C(=O)O)NC1=O NPYMOMKXKZUXGG-UHFFFAOYSA-N	
DK-metribuzin glucuronide conjugate, M16, Glucuronide-conjugate (of DK) #9	3-[(6-*tert*-butyl-3,5-dioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)amino]-3-deoxyhexopyranuronic acid OC1C(NN2C(=O)C(=NNC2=O)C(C)(C)C)C(O)C(OC1O)C(=O)O PDOLDXBUGCKOLV-UHFFFAOYSA-N	

(a): The 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, 07 July 2021).
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 August 2021).