CONCLUSION ON PESTICIDES PEER REVIEW

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Updated peer review of the pesticide risk assessment of the active substance trinexapac (variant evaluated trinexapac-ethyl)

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Abstract

The conclusions of the European Food Safety Authority (EFSA) following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State, Lithuania, and co-rapporteur Member State, Latvia, for the pesticide active substance trinexapac and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative use of trinexapac as a plant growth regulator on barley (winter and spring) and wheat (winter). MRLs were assessed in rye. The conclusions were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in January 2019.The reliable end points, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. The confirmatory data following the review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 were also assessed under this conclusion. Missing information identified as being required by the regulatory framework is listed. Concerns are reported where identified.

Keywords: trinexapac, trinexapac-ethyl, peer review, risk assessment, pesticide, plant growth regulator

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Summary

Commission Implementing Regulation (EU) No 844/2012 (hereinafter referred to as 'the Regulation') 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. Trinexapac is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of the Regulation, the rapporteur Member State (RMS), Lithuania, and co-rapporteur Member State (co-RMS), Latvia, received an application from the EU Task force of trinexapac-ethyl consisting of the Task Force members Syngenta Crop Protection AG, Adama Agriculture BV, Cheminova A/S and Helm AG, for the renewal of approval of the active substance trinexapac. In addition, the EU Task force of trinexapac-ethyl submitted an application for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicants, the co-RMS (Latvia), the European Commission and the European Food Safety Authority (EFSA) about the admissibility.

The RMS provided its initial evaluation of the dossier on trinexapac-ethyl in the renewal assessment report (RAR), which was received by EFSA on 31 March 2017. The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005. In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, the EU Task force of trinexapac-ethyl consisting of the Task Force members Syngenta Crop Protection AG, Adama Agriculture BV, Cheminova A/S and Helm AG, for comments on 18 April 2017. 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 24 July 2017.

Following consideration of the comments received on the RAR, 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.

In accordance with Article 13(1) of the Regulation, EFSA should adopt a conclusion on whether trinexapac can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council and give a reasoned opinion concerning MRL applications as referred to in Article 10(1) of Regulation (EC) No 396/2005.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative use of trinexapac-ethyl as a plant growth regulator on barley (winter and spring) and wheat (winter), as proposed by the applicant. MRLs were assessed in rye. In addition, the conclusions from 2018 (EFSA, 2018) were updated with regard to the endocrine-disrupting properties following a mandate received from the European Commission in January 2019. Full details of the representative uses and the proposed MRLs can be found in Appendix A of this report.

Data were submitted to conclude that the representative uses of trinexapac-ethyl proposed at EU level result in a sufficient efficacy as a plant growth regulator.

A data gap was identified for a search of the scientific peer-reviewed open literature to include the metabolites CGA224439 and M2 and for a search of pertinent environmental metabolites.

Data gaps were identified in the area of **identity physical–chemical properties** for the determination of the content of the relevant impurity in the formulation and for 5-batch data for the content of two possible relevant impurities in one source.

In the area of **mammalian toxicology** and non-dietary exposure, further data are needed to address the toxicological profile of some metabolites and impurities.

In the area of **residues**, several data gaps were identified and the consumer risk assessment is not finalised. The provisional dietary risk assessment resulted in consumer exposure below the toxicological reference value. The representative use on barley is not sufficiently supported by residue trials. The non-representative use on rye is supported by data and a change of the existing MRL is not required. Confirmatory data requirement on beans with pods identified in the MRL review is fully addressed only for the use in Southern Europe.

In the area of **environmental fate and behaviour,** a data gap was identified for information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface and groundwater, when surface water or groundwater is abstracted for 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, a data

gap was identified for the identity of the aqueous photolysis metabolite WaterM3Photolysis, which was only characterised as being a structural isomer of trinexapac-ethyl.

In the area of **ecotoxicology,** data gaps were identified for further information to address the risk to birds and mammals for trinexapac-ethyl metabolites and the risk to honeybees for trinexapac-ethyl and its metabolites.

The technical specification is not supported from the (eco)toxicological point of view leading to a critical area of concern.

Regarding the assessment of the **endocrine disruption (ED) properties** for humans and non-target organisms, based on the available evidence, the ED criteria according to points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, are not met for the EATS-modalities.

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Background

Commission Implementing Regulation (EU) No 844/2012[1] (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[2]. 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 up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS, Lithuania, and co-RMS, Latvia, received an application from the EU Task force of trinexapac-ethyl consisting of the Task Force members Syngenta Crop Protection AG, Adama Agriculture BV, Cheminova A/S and Helm AG, for the renewal of approval of the active substance trinexapac. In addition, EU Task force of trinexapac-ethyl submitted an application for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[3]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Lithuania), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on trinexapac-ethyl in the RAR, which was received by EFSA on 31 March 2017 (Lithuania, 2017). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, the EU Task force of trinexapac-ethyl, for consultation and comments on 31 March 2017. 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 24 July 2017. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 1 September 2017. 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.

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.

[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] 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.

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

A final consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in February 2018, leading to the finalisation of the EFSA Conclusion (EFSA, 2018).

Commission Regulation (EU) 2018/605[4] introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the approval/renewal of active substances, including pending applications. The peer review on the active substance trinexapac was already completed at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the ECHA/EFSA guidance (2018) document[5] for this substance was not available.

Since on the basis of the EFSA Conclusion published on 13 April 2018, it was not possible for risk managers to conclude whether or not the active substance trinexapac is an endocrine disruptor, in January 2019, the European Commission requested EFSA to re-assess the information and update its Conclusion on the ED potential of the substance in accordance with the new criteria. For this purpose, EFSA has performed an assessment of the ED properties of the active substance trinexapac in line with the EFSA/ECHA (2018) guidance for further consideration in the peer review.

In the context of this process, following a consultation with Member States in the Pesticide Peer Review Experts' Meeting TC 10 Mammalian toxicology – Ecotoxicology joint session (July 2019), it was concluded that trinexapac-ethyl does not meet the ED criteria for humans for the thyroid (T) modality according to point 3.6.5 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605. However, additional testing was required to complete the current data package about the oestrogen, androgen and steroidogenesis (EAS)-mediated adverse effects in relation to human health and to further investigate the ED properties of the substance for non-target organisms. Therefore, in accordance with the provisions of Commission Regulation (EU) No 2018/1659[6], in August 2019, the applicant was given the opportunity to submit, within a period of 30 months, additional information to address the approval criteria set out in points 3.6.5 and 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) No 2018/605, and/or documentary evidence demonstrating that trinexapac-ethyl may be used such that exposure is negligible, and/or the conditions for application of the derogation under Art.4(7) of Regulation (EC) No 1107/2009 are met. The additional information submitted by the applicant was subsequently evaluated by the RMS.

A public consultation on the revised RAR on the endocrine properties assessment made available by the RMS after the 30-month clock stop (Lithuania, May 2022) was conducted in June–August 2022. All comments received, including those from the applicant and Member States, were collated in the format of a reporting table and were considered during the finalisation of the peer review. As a result of the public consultation, the need for an additional expert's consultation in the area of ecotoxicology was raised.

In the context of this process, a consultation with Member States in the Pesticide Peer Review Meeting TC 93 Ecotoxicology on ED took place in January 2023.

A final consultation on the updated conclusions arising from the peer review following the mandate from the European Commission took place with Member States via a written procedure in April–May 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 trinexapac as a plant growth regulator on barley (winter and spring) and wheat (winter) as proposed by the applicant. MRLs were assessed in rye. Confirmatory data following the review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 were also assessed. In addition, the conclusions were updated with regard to the endocrine-disrupting properties following the ad hoc mandate received from the European Commission in January 2019. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

[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.

[5] ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S, 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.

[6] Commission Implementing Regulation (EU) 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. OJ L 278, 8.11.2018, p. 3–6.

In addition, a key supporting document to this updated 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 September 2017 and 25 August 2022[7]);
- the evaluation table (5 March 2018, updated in May 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 EFSA endocrine disruption (ED) assessment (July 2019)[8];
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Lithuania, 2018, updated 2022, updated 2023), the evaluation report on confirmatory data under Article 12 of Regulation (EC) No 396/2005 (Lithuania, 2016), the Peer Review Report and the EFSA ED assessment (EFSA, 2019), all these 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 formulated product

Trinexapac is the ISO common name for (1*RS*,4*EZ*)-4-[cyclopropyl(hydroxy)methylene]-3,5-dioxocyclohexanecarboxylic acid (IUPAC). Trinexapac-ethyl, a derivative of trinexapac, is the modified ISO common name for ethyl (1*RS*,4*EZ*)-4-[cyclopropyl(hydroxy)methylene]-3,5-dioxocyclohexanecarboxylate (IUPAC).

The representative formulated product for the evaluation was 'A8587F (Moddus ME)' a micro-emulsion formulation (ME) containing 250 g/L trinexapac-ethyl. An FAO specification is not available for this substance.

The representative uses evaluated were spray applications for the prevention of lodging in winter and spring barley and in winter wheat in the EU. Full details of the GAPs can be found in the list of end points in Appendix A.

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

A 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, was conducted in accordance with EFSA guidance (EFSA, 2011). However, a data gap has been identified for a search of the scientific peer-reviewed open literature to include the metabolite CGA224439 in the mammalian toxicology section and for a search on the metabolite M2 in the fate section. In the ecotoxicology section, most of the relevance criteria applied for the literature review were not agreed upon. In addition, some of the pertinent environmental metabolites were not covered by the search and this led to a data gap.

[7] Reporting table following consultation on the revised RAR on the assessment of the endocrine-disrupting properties made available after the 30-month clock stop.

[8] ED assessment performed by EFSA before the timepoint of the ED additional information request (stop of the clock). The ED assessment including evaluation of the newly provided additional information on the endocrine disruption properties following the ED clock stop is available in the revised RAR (Lithuania, 2023) with the final outcome presented in the current EFSA Conclusion (see Section 6).

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: SANCO/3029/99-rev. 4 (European Commission, 2000a), SANCO/3030/99-rev. 4 (European Commission, 2000b), SANCO/10597/2003-rev. 10.1 (European Commission, 2012) and SANCO/825/00-rev. 8.1 (European Commission, 2010).

It should be noted that the evaluation was based on data belonging to the variant trinexapac-ethyl.

The proposed specifications for trinexapac-ethyl are based on batch data from industrial scale production. There was not an agreement between the members of the task force on a common specification of the technical material. The minimum purity of the active substance as manufactured is 950 g/kg for Syngenta, 960 and 977 g/kg for Cheminova A/S sources, 970 g/kg for Helm AG and 970 and 980 g/kg for Adama Agriculture BV sources. Toluene was considered relevant impurity with a maximum amount of 3 g/kg. CGA158377 was considered relevant impurity with a maximum amount of 6 g/kg. A data gap was also identified for 5-batch data for the content of two possible relevant impurities of the batches, relevant for Adama Agriculture BV. It is proposed to update the reference specification as the specification for the first approval did not consider these relevant impurities and also the maximum content of the impurities had been regarded as provisional. An FAO specification is not available.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of trinexapac-ethyl or the representative formulation. The main data regarding the identity of trinexapac-ethyl and its physical and chemical properties are given in Appendix A.

Adequate methods are available for the generation of pre-approval data required for the risk assessment. Methods of analysis are available for the determination of the active substance and the relevant impurity toluene in the technical material and in the representative formulation. A data gap was identified for a method for the determination of CGA158377 (ethyl (1RS)-ethyl 3-hydroxy-5-oxocyclohex-3-ene-1-carboxylate) in the formulation.

The residue definition for monitoring in plant and animal matrices was defined as sum of trinexapac and its salts, expressed as trinexapac. The QuEChERS multi-residue enforcement method and also single residue methods with LC–MS/MS can be used for the determination of residues of trinexapac in food and feed of plant and animal origin with a limit of quantification (LOQ) of 0.01 mg/kg in each commodity group and in each animal matrix.

Appropriate HPLC–MS/MS method exists for monitoring trinexapac-ethyl in soil with LOQ of 0.01 mg/kg. Trinexapac-ethyl and trinexapac can be monitored in surface, ground and drinking water with an LOQ of 0.05 μg/L for each compound. Residues of trinexapac-ethyl in air can be determined by HPLC–MS/MS with an LOQ of 10 $\mu g/m^3$.

Monitoring trinexapac in body fluids is possible with the QuEChERS method with HPLC–MS/MS with an LOQ of 0.01 mg/kg.

2. Mammalian toxicity

The toxicological profile of trinexapac-ethyl and its metabolites was discussed at the Pesticides Peer Review Experts' Meeting 170 (December 2017). The assessment was based on the following guidance documents: SANCO/221/2000 – rev. 10-final (European Commission, 2003), SANCO/10597/2003 – rev. 10.1 (European Commission, 2012), Guidance on Dermal Absorption (EFSA PPR, 2012) and Guidance on the Application of the CLP Criteria (ECHA, 2015).

To assess the toxicological profile of the **active substance,** the different applicants submitted a set of valid toxicity studies. The assessment relied on the most robust data package submitted by Syngenta Crop Protection AG. However, a conclusion on whether the batches used in the toxicity studies submitted by Syngenta Crop Protection AG were representative of the proposed Syngenta's technical specification could not be drawn leading to a critical area of concern. This is because further data are needed to confirm the purity content of batches used in toxicity studies and because further data would be needed to exclude the relevance of impurities 5 and 9 (i.e. potentially relevant considering QSAR alerts for genotoxicity) or to support their maximum content if impurities 5 and 9 would finally be considered genotoxic (data gap). The impurities CGA158377 and toluene are

considered relevant based on their hazard (skin sensitisation and reproductive toxicity, respectively; maximum content 6 g/kg and 3 g/kg, respectively). Once the representativeness of the Syngenta Crop Protection AG's technical specification is supported by toxicity studies, further assessment of the equivalence between technical materials of different applicants should be done (data gap).

In the toxicokinetics studies, trinexapac-ethyl was extensively and rapidly absorbed. Oral absorption was estimated to be greater than 96%. There was no evidence for accumulation. Excretion of substance was predominantly through the urine. The main metabolic pathway identified was hydrolysis to trinexapac (CGA179500). *In vitro* metabolic patterns in the human and rat species were similar. No unique human metabolite expected.

In the acute toxicity studies, trinexapac-ethyl has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant but a skin sensitiser.[9]

Trinexapac-ethyl is not phototoxic in vitro. The lack of activity in the phototoxicity study supports the view that trinexapac-ethyl would be inactive in a photomutagenicity assay.

The critical effects in short-term oral toxicity studies with rats and dogs, included histopathology changes in the kidney in rats and clinical signs and changes in uterus weight, oestrous cycling, cerebral vacuolation and haematological findings in dogs. Non-specific critical effects as reduced terminal body weight were also observed in male dogs. The relevant short-term oral no observed adverse effect levels (NOAELs) are 32 mg/kg body weight (bw) per day (1-year dog study) and 34 mg/bw per day (90-day rat study).

The majority of experts in the peer review meeting considered that the evidence from an *in vitro* gene mutation assays supports that trinexapac-ethyl is not mutagenic *in vitro* and no further *in vivo* tests (e.g. TGR assay) are justified. Based on a negative *in vivo* micronucleous test where sufficient evidence of bone marrow exposure was demonstrated from toxicokinetic studies, the experts concluded that trinexapac-ethyl is unlikely to be genotoxic *in vivo*.

In long-term toxicity and carcinogenicity studies with rats and mice, the target organ of toxicity was the mammary skin, kidney and liver in rats whereas no adverse effects were observed in mice. The rat was the most sensitive species. Trinexapac-ethyl showed no carcinogenic potential in both species. The relevant long-term NOAEL is 116 mg/kg bw per day (2-year rat study).

In reproductive toxicity studies, fertility and overall reproductive performance was not impaired. Parental and offspring toxicity included reduced body weight gain and reduced body weight, respectively. Reduced survival index was also observed in pups. The relevant parental, reproductive and offspring NOAELs are 106.2, 1,293 and 662.9 mg/kg bw per day, respectively. During the peer review meeting experts discussed the potential of developmental toxicity for trinexapac-ethyl based on the increased incidence of asymmetrically shaped sternebrae (grey zone anomaly) observed at the top dose level of 1,000 mg/kg bw per day in the rat developmental toxicity study. Whereas the experts agreed that for the risk assessment, this finding should be considered to set the NOAEL at 200 mg/kg bw per day, no consensus was reached regarding a proposal from the peer review on classification and labelling.[9] The RMS did not support classification and labelling.

In rats, no potential for neurotoxicity was observed in the standard toxicity and specific neurotoxicity studies. However, neurotoxicity was observed in standard toxicity studies with dogs. The analysis of biological relevance of the findings showed that compounds disturbing the metabolism of glucose induced similar swelling of astrocytes and oligodendroglia (cerebral vacuolation). The experts supported the RMS's view that in the absence of mechanistic studies and/or any human data, cerebral vacuolation observed in dogs should be considered relevant for humans.

No evidence of immunotoxicity was observed in the general toxicity studies and in the 28 day immunotoxicity study in mice.

The experts agreed to keep the existing toxicological reference values (European Commission, 2006). The acceptable daily intake (ADI) is 0.32 mg/kg bw per day, on the basis of the relevant NOAEL of 31.6 mg/kg bw per day in the 1-year study in dogs based on reduced terminal body weight, clinical signs, uterus weight, oestrous cycling, brain and haematological changes at 366 mg/kg bw per day.

An uncertainty factor of 100 was applied. An acute reference dose (ARfD) is not needed for the substance. The systemic acceptable operator exposure level (AOEL) is 0.34 mg/kg bw per day on the basis of the relevant short-term NOAEL of 34 mg/kg bw per day in the 90-day study in rats based on histopathology changes in the kidney at 346 mg/kg bw per day. An uncertainty factor of 100 was

[9] It is noted that trinexapac-ethyl has harmonised classification as STOT RE 2, H373 (gastrointestinal tract) and Skin Sens. 1B, H317 in accordance with the Commission Delegated Regulation (EU) 2021/849 of 11 March 2021 (17ATP).

applied. No correction factor for oral absorption is needed to derive the AOEL. The experts agreed that no systemic acute acceptable operator exposure level (AAOEL) was needed for trinexapac-ethyl.

The RMS estimated **non-dietary exposure**[10] (i.e. for operators, workers, bystanders and residents) considering dermal absorption values of trinexapac-ethyl in 'Trinexapac-ethyl 250 g/L ME' of 25% for the concentrate and of 75% for the dilution as input values (default values, EFSA PPR Panel, 2012).

Considering the representative uses with 'Trinexapac-ethyl 250 g/L ME' as plant growth regulator in cereals, the maximum estimated operator exposure was below the AOEL (35.9% of the AOEL) without the use of personal protective equipment (PPE) during mixing and loading and application according to the German Model. Re-entry worker exposure was below the AOEL without the use of PPE (11.0% of the AOEL). Bystander and resident exposure was below the AOEL (maximum 1.6% of the AOEL; children bystander).

Available information on the toxicological profile of **metabolites** indicated that CGA313458 is unlikely to be genotoxic. Further data on repeated exposure might be needed pending clarification on relevance of metabolite in processing commodities (see Section 3). CGA224439 is not genotoxic. It is considered of higher toxicity than the parent compound based on 90-day rat toxicity study available to JMPR (JMPR, 2014) which was not submitted to the RMS for an independent assessment. A data gap is proposed to address the repeated exposure toxicity and updated literature search to include this metabolite. Hydroxylated CGA179500 (SYN54584) is considered covered by trinexapac (CGA179500) as well as by trinexapac-ethyl (i.e. at least as toxic as the parent). Tricarballylic acid (CGA275537) showed a higher acute oral toxicity than the parent. There would be no sufficient data for a final conclusion on genotoxicity and no data for repeated exposure (comparison to parent or specific references values) are available. However, considering the natural occurrence of tricarballylic acid, further data are not needed (see Section 3). The metabolite CGA300405 is unlikely to be genotoxic. Further data on repeated exposure might be not needed pending on further data to confirm the rapid hydrolysis to tricarballylic acid (see Section 3). CGA329773 is unlikely to be genotoxic and repeated toxicity data indicated less toxic than parent. CGA158377 and CGA113745 are unlikely to be genotoxic. Repeated toxicity data indicate comparable toxicity than parent.

3. Residues

3.1. Representative use residues

Trinexapac was discussed at the Pesticides Peer Review Experts' meeting 171 on residues.

The assessment in the residue section is based on the OECD guidance document on overview of the residue chemistry studies (OECD, 2009), the OECD publication on the MRL calculations (OECD, 2011), the European Commission guideline document on the MRL setting and on comparability and extrapolation (European Commission, 2011, 2017) and the Joint Meeting on Pesticide Residues (JMPR) recommendations on livestock burden calculations (JMPR, 2004, 2007).

All the metabolism studies were conducted exclusively with trinexapac-ethyl radiolabelled in the cyclohexyl ring and not in the cyclopropyl moiety. Cleavage of the molecule was observed and confirmed in the hydrolysis study with formation of the compound CGA224439. There are indications that CGA224439 may be more toxic than parent (see Section 2). A data gap is identified to address the nature of residues in primary and rotational crops and livestock with regard to the cyclopropyl moiety. Primary plant metabolism was investigated on cereal/grass (wheat, rice, grass) and pulse/ oilseed (rape seeds). In grains and seeds trinexapac, free and in the conjugated form, was the main component of the total residues followed by its hydroxylated form (12% total radioactive residue (TRR), 0.17 mg/kg). The Task Force communicated that this metabolite (SYN548584) is unstable outside plant matrix and is not possible to be analysed. Therefore, the Task Force proposed to estimate its amounts in cereals using a conversion factor derived from the metabolism study in wheat. Overall, further data to elucidate the structure and amounts of SYN548584 in cereals grain and straw are required (data gap). In the plant parts intended for animal feed, metabolism was more extensive. Trinexapac and the metabolite CGA300405 were both present at comparable levels (max. 22% and 21% TRR, respectively) in forage and straw. Tricarballylic acid (CGA275537) was identified in wheat, rice and grass at varied proportions and levels (19% TRR, 0.03 mg/kg, rice straw; 14% TRR, 0.28 mg/kg, grass forage) whereas aconitic acid (CGA312753) was only identified in rice husk (35% TRR, 0.06 mg eq/kg).

[10] In the RAR, the RMS also presented exposure calculations according to EFSA Guidance on non-dietary exposure (EFSA, 2014).

As they are also naturally occurring compounds in plants and, moreover, tricarballylic acid seems to be produced by rumen microorganisms, they were not proposed for inclusion in the residue definition for feed items. In grass, unique metabolites were observed compared to the other cereal crops and a data gap is identified to address their relevance for the entire category of cereal/grass crops. In the rotational crop metabolism studies, residues were too low (total residues quantifiable only in wheat foliage and lettuces at 30 days plant back interval) to define the metabolic pathway of trinexapac.

For the cereal/grass crops category group, the residue definition for monitoring is trinexapac and its salts, expressed as trinexapac (current residue definition). For risk assessment, the residue definition shall be regarded as provisional and it is proposed as trinexapac, free and conjugated for grains and trinexapac, free and conjugated plus CGA300405 for cereal fodder items/grass. Whether the consumer risk assessment for CGA300405 is to be conducted combined or separately is pending assessment of its toxicological relevance (see Section 2) and investigation to address the relevance in feed items and the potential carry-over of residues in animal commodities (data gap). For the pulse and oilseed group, the residue definition could not be finalised.

A residue definition for processed products could not be set due to the contradictory outcome of the standard hydrolysis studies. These experiments showed the compound to be either stable or to degrade forming CGA113745, CGA313458 and CGA224439, leading to a data gap for further clarifications.

Scrutiny of residue trials for independency and stability of samples resulted in the exclusion of some of the available trials from the assessment. Nevertheless, a sufficient number of residue trials were still available to derive a MRL proposal for the representative use on wheat, but not for the use on barley. Pending the finalisation of the residue definitions in cereal/grass, products of animal origin and processed products, additional residue data in raw and processed commodities may be required. These trials should analyse for the individual components in the residue definition for risk assessment, and in supported by demonstrated storage stability and/or storage stability for the individual components of the residue definition for risk assessment covering the maximum storage time period of the trial samples (data gap).

Metabolism studies with trinexapac-ethyl in lactating goats and laying hens showed that trinexapac is the main component of total residues. The only major metabolite identified is CGA113745 in goat liver (16.3% TRR, 0.35 mg/kg). For monitoring, the residue definition is proposed as trinexapac and its salts, expressed as trinexapac. Meanwhile, for risk assessment, the residue definition is provisionally set in poultry as trinexapac and in ruminants as trinexapac plus the metabolite CGA 113745, expressed as trinexapac. In the feeding study in lactating cows, the metabolite CGA 113745 has not been analysed for. Based on the results, residues of trinexapac are not expected in ruminant tissues and milk. Significant residues are not expected in poultry commodities as well considering the outcome of the metabolism study. Recalculation of the livestock dietary burden is pending the finalisation of the residue definition for the risk assessment for feed items and in animal products and information on the transfer of residues of CGA300405 and SYN548584 in animal matrices. Feeding studies analysing for CGA113745 in tissues and milk of ruminants may be required. The relevance of the residues in the fish diet and information against the data requirements on fish (data gap) as well as residues in pollen and bee products for human consumption are required (data gap).

A provisional consumer risk assessment was carried out using the EFSA PRIMo rev.2 model considering the representative use on wheat. This provisional assessment resulted in consumer exposure of 1.3% of the ADI. An acute consumer exposure assessment is not necessary.

It is noted that the residue definition for risk assessment of cereals and products of animal origin has been changed compared to the residue definitions agreed in the review of the existing MRLs for trinexapac (MRL review) due to availability of new metabolism studies. Upon final decision on the residue definitions for risk assessment, the overall consumer exposure and risk assessment may need to be revised.

3.2. Maximum residue levels and confirmatory data MRL review

The request to evaluate the MRL for rye which was included in the application for renewal is supported by extrapolation from the data on wheat. A change of the MRL of 0.5 mg/kg set in Regulation (EC) No 396/2005 is not required.

EFSA evaluated additional residue data on beans with pods as requested during the MRL review. Overall, seven northern (NEU) and eight southern (SEU) Europe residue trials conducted with a micro-emulsion (ME) formulation are available. Risk managers may decide to confirm the tentative

MRL value or to decrease the level to 9 mg/kg based on the complete data set of SEU residue trials. An update of the consumer risk assessment is not necessary.

Confirmatory data requirement on beans with pods identified in the MRL review EFSA, 2012 is fully addressed only for the use in Southern Europe.

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, trinexapac-ethyl exhibited very low persistence, forming the major (> 10% applied radioactivity (AR)) metabolite CGA179500 (max. 93.1% AR), which exhibited low to moderate persistence. Mineralisation of different 14C radiolabel positions to carbon dioxide accounted for 58.0% AR after 90 days to 84.6% AR after 28 days. The formation of unextractable residues for these radiolabels accounted for 6.8% AR after 90 days and 10–31% AR after 28 days (not extracted by acetonitrile/ water) and accounted for 32.9% AR after 60 days (not extracted by acetonitrile buffered at room temperature followed by acetonitrile/ammonium acetate at 60°C). In anaerobic soil incubations, degradation of trinexapac-ethyl was fast, with the degradation pathway similar to that under aerobic conditions. In a photolysis study trinexapac-ethyl exhibited very low persistence, forming under dry conditions the major (> 10% applied radioactivity (AR)) metabolites CGA179500 (max. 22.8% AR) and metabolites CGA300405 (max. 12.5% AR) and CGA275537 (max. 10.8% AR), which exhibited very low persistence, and forming under moist conditions the major metabolites CGA179500 (max. 61.5% AR) and CGA275537 (max. 6.5% AR).

Trinexapac-ethyl and the metabolite CGA179500 exhibited high to low mobility in soil. The metabolite CGA275537 exhibited very high to low mobility in soil. It was concluded that the adsorption of trinexapac-ethyl and its metabolites was pH dependent. The lowest Kfoc values related to soils with pH > 7 were considered as worst-case values and used for exposure assessment. Reliable mobility data could not be generated for the metabolite CGA300405 due to its high instability in soil. Therefore, the Kfoc was determined using the quantitative structure–property relationships (QSPR) method (using KOCWIN™).

In laboratory incubations in dark aerobic natural sediment water systems, trinexapac-ethyl exhibited low persistence, forming the major metabolite CGA179500 (max. 64% AR in water and 6.9% AR in sediment), exhibiting moderate persistence. The unextractable sediment fraction of 14C-trinexapac-ethyl accounted for 16–27% AR at end of the study (111 days). Mineralisation was the major sink for this radiolabel accounting for 59–69% AR at the end of the study. In a laboratory sterile aqueous photolysis study, trinexapac-ethyl was fast degraded forming the major (> 10% applied radioactivity (AR)) metabolites CGA300405 (max. 41% AR), M2 (max. 17.9% AR) and WaterM3Photolysis (max. 16.9% AR). The identity of the aqueous photolysis metabolite WaterM3Photolysis was not known and it was only characterised as being a structural isomer of trinexapac-ethyl. This has led to the identification of a data gap (see Section 7). Irradiation of 14C-trinexapac-ethyl in sterile natural water resulted in the formation of one major photodegradation product CGA300405 (max. 83.4% AR). The necessary surface water and sediment exposure assessments (Predicted environmental concentrations (PEC) calculations) were carried out for trinexapac-ethyl and the metabolites CGA179500, CGA300405, CGA275537, M2 and WaterM3Photolysis (without the identity being confirmed), using the FOCUS (FOCUS, 2001) step 1 and step 2 approach (version 3.2 of the Steps 1–2 in FOCUS calculator).

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (FOCUS, 2009) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.4 for trinexapac-ethyl and the metabolites CGA179500, CGA300405 and CGA275537. The potential for groundwater exposure from the representative uses of trinexapac-ethyl 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 trinexapac-ethyl and these metabolites.

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

A data gap has been identified for a search of the scientific peer-reviewed open literature on the metabolite M2.

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

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013). According to Regulation (EU) No 283/2013[11], data should be provided regarding the acute and chronic toxicity to honeybees and data to address the development of honeybee brood and larvae. As the European Commission (2002a) does not provide a risk assessment scheme which is able to use the chronic toxicity data for adult honeybees and the honeybee brood, when performing the risk assessment according to that guidance document, the risk to adult honeybees from chronic toxicity and the risk to bee brood, could not be finalised due to the lack of a risk assessment scheme. Therefore, the EFSA (2013) was used for risk assessment in order to reach a conclusion for the representative uses.

Some aspects of the risk assessment of trinexapac-ethyl were discussed at the Pesticide Peer Review teleconference 160.

The technical material specification proposed was not comparable to the material used in the ecotoxicological testing and this leads to a critical area of concern.

It is noted that the some ecotoxicological tests were performed with the formulation 'A8587F', this was considered acceptable since this is a water-based (ME) formulation comparable to the representative one (A8587B). It is additionally noted that various ecotoxicological studies were performed with the formulation 'A 7725 M (250 EC)'. The comparability of this formulation with the representative formulation could not be fully demonstrated; therefore, the available studies with this formulation were considered as supportive only.

A low acute and long-term risk to **birds** and **wild mammals** for trinexapac-ethyl was concluded for all routes of exposure and for all the representative uses. The available data were not sufficient to address the risk to birds and mammals for some of the trinexapac-ethyl metabolites (data gap).

A low acute and chronic risk to **aquatic organisms** was concluded for trinexapac-ethyl and all its pertinent surface water metabolites.

Suitable acute (oral and contact) and chronic (adult and larvae) toxicity studies on honey**bees** were available. Information on potential sublethal effects of trinexapac-ethyl on honeybees (e.g. effects on hypopharygeal glands (HPG)) was not available (data gap). A low risk was concluded for all the representative uses with the available toxicity data for a risk assessment performed in line with EFSA guidance document on bees (EFSA, 2013). A risk assessment for exposure via contaminated water (surface water and puddle water) was not provided (data gap). A high acute and chronic (adult and larvae) risk to honeybees from exposure to guttation water could not be excluded (data gap). A suitable assessment for accumulative effects was not available. The available information was not sufficient to address the risk to honeybees from metabolites occurring in pollen and nectar (data gap). No data were available for bumblebees and solitary bees.

A low risk to **non-target arthropods** was concluded for trinexapac-ethyl for all the representative uses. A low risk **to earthworms** and other **soil macro- and microorganisms** was concluded for trinexapac-ethyl and its pertinent metabolites for all the representative uses.

With regard to **non-target terrestrial plants**, it is noted that the data set included valid studies performed with the active substance, non-GLP screening studies performed with the representative formulation and studies performed with the formulation 'A 7725 M (250 EC)'. Considering the endpoints obtained from the studies performed with the active substance, a low risk could be concluded. Considering that the endpoints available with the formulated products did not demonstrate a higher toxicity of the formulated products, a low risk to non-target plants was concluded for all the representative uses.

A low risk for trinexapac-ethyl for **biological methods of sewage treatment** was concluded.

A literature search in line with the EFSA guidance (EFSA, 2011) was performed; however, some of the pertinent environmental metabolites were not covered by the search (data gap). It is noted that the RMS considered the literature search comprehensive and the methodology suitable.

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

6. Endocrine disruption properties

Trinexapac-ethyl was discussed at the Pesticides Peer Review Experts' Meeting 10 (Mammalian Toxicology and Ecotoxicology, July 2019) and at the Pesticides Peer Review Experts' TC 93 (Ecotoxicology, January 2023).

With regard to the assessment of the endocrine disruption (ED) potential of trinexapac-ethyl for **humans** according to the ECHA/EFSA guidance (2018), in determining whether trinexapac-ethyl interacts with the oestrogen, androgen and steroidogenic (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 trinexapac-ethyl with the EAS and T signalling pathways using the available evidence in the dataset.

For the EATS modalities, the data set is complete, and no adversity has been observed. Therefore, in line with ECHA/EFSA guidance (2018), scenario 1a is applicable for the T modality (ED criteria not met because there is no 'EATS-mediated' adversity) and scenario 2a(ii) is applicable for the EAS modalities (ED criteria not met because no endocrine activity has been observed for the EAS modalities) and trinexapac-ethyl is not considered to meet the ED criteria 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.

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

For non-target organisms other than mammals, a Fish Short-Term Reproduction Assay (FSTRA, OECD TG 229) and an Amphibian Metamorphosis Assay (AMA, OECD TG 231) were made available.

The FSTRA was discussed at the Pesticides Peer Review Experts' meeting TC 93.[12] Overall, all experts agreed that the study design was appropriate and that there were no treatment-related findings. The AMA did not show any evidence suggesting T-mediated endocrine activity.

Based on the above considerations, trinexapac-ethyl is not considered to meet the ED 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 for the EATS-modalities.

[12] Experts' consultation 5.3 of the Peer Review meeting report TC 93 (20 January 2023), Trinexapac-ethyl.

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)	Persistence	Ecotoxicology
Trinexapac-ethyl	Very low persistence Single first order and bi-phasic kinetics DT_{50} 0.04–0.72 days (DT_{90} 0.15–2.4 days; laboratory conditions at 20–25°C, pF2–75% FC)	Low risk
CGA179500	Low to moderate persistence Single first-order kinetics DT_{50} 1.0–32 days (DT_{90} 3.3–106 days; laboratory conditions at 20–25°C, pF 2–75% FC)	Low risk
CGA300405	Very low persistence Bi-phasic kinetics DT_{50} 0.03–0.08 days (DT_{90} 0.37–1.71 days; laboratory conditions at 20°C, pF 2)	Low risk
CGA275537	Very low persistence Single first-order kinetics DT_{50} 0.17–0.27 days (DT_{90} 0.56–0.91 days; laboratory conditions at 20°C, pF 2)	Low risk

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[(a)]	Pesticidal activity	Toxicological relevance
Trinexapac-ethyl	High to low mobility K_{Foc} 60–629 mL/g	No	Yes	Yes
CGA179500	High to low mobility K_{Foc} 145–609 mL/g	No	Yes	Assessment not triggered
CGA300405	Very high mobility K_{Foc} 1.0 mL/g (estimated by QSPR method)	No	No data	Assessment not triggered
CGA275537	Very high to low mobility K_{Foc} 4.3–1241 mL/g	No	No data	Assessment not triggered

(a): FOCUS scenarios or relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Trinexapac-ethyl	Low risk
CGA179500 (soil, surface water)	Low risk
CGA300405 (soil, aqueous photolysis)	Low risk
CGA275537 (soil)	Low risk
M2 (aqueous photolysis)	Low risk
WaterM3Photolysis (aqueous photolysis)	Low risk

Table 4: Air

Compound (name and/or code)	Toxicology
Trinexapac-ethyl	Low acute inhalation toxicity to rats (Rat LC_{50} inhalation > 5.3 mg/L air per 4 h (nose only, liquid aerosol)).

8. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- A search of the scientific peer-reviewed open literature to include the metabolites CGA224439 and M2 and for a search of pertinent environmental metabolites (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2, 4, 5).
- Analytical method for the determination of the relevant impurity CGA158377 (ethyl (1*RS*)-ethyl 3-hydroxy-5-oxocyclohex-3-ene-1-carboxylate) in the formulation (relevant for representative uses evaluated with formulation A8587F; submission date proposed by the applicant: unknown; see Sections 1 and 2).
- Five-batch data for the content of two possible relevant impurities of the batches, relevant for Adama Agriculture BV (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Confirmation of the purity content of toxicity studies (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Further data either to exclude the relevance of impurities 5 and 9 or to support an acceptable maximum content for these impurities in the technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Equivalence between technical materials once a specification is supported by toxicity studies (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- 90-day rat study on CGA224439 available to JMPR to address the repeated exposure toxicity (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- The nature of residues in primary crops for at least the representative use, in rotational crops and in livestock with regard to the cyclopropyl moiety and further attempt to elucidate/confirm the structure and amounts of the metabolite SYN548584 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Further information to address the relevance of unique metabolites identified in the grass (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- The relevance in feed items and the potential carry-over of residues in animal commodities of the major feed metabolite CGA300405 including evidence of fast hydrolysis to tricarballylic acid (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Sections 2 and 3).
- Further clarification to explain the contradictory findings (stability vs. instability) in the standardised hydrolysis experiments to address nature of residues in processing commodities (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Additional residue data in barley and in wheat straw from independent field trials compliant with the GAP and in processed commodities supported by demonstrated storage stability and/ or storage stability for each individual component of the residue definition for risk assessment in cereal/grass and processed products covering the maximum length of storage of the trial samples (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Relevance of residues in the fish diet and information against the residues data requirements on fish (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 3).
- Residues in pollen and bee products for human consumption resulting from residues taken up by honeybees from crops at blossom with regard to trinexapac and its degradation products (relevant for all representative uses evaluated; submission date proposed by the applicant:1Q18; see Section 3).

- The identity of the aqueous photolysis metabolite WaterM3Photolysis only formed in buffer solution (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown; see Section 4).
- Information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface and groundwater, when surface water or groundwater are abstracted for drinking water, were not sufficient in order to assess the consumer risk from the consumption of drinking water (relevant for all representative uses evaluated, submission date proposed by the applicant: unknown; see Section 4).
- Further information is needed to address the risk to birds and mammals for the plants metabolites SYN548584, CGA351210, SYN540406, NOA433257, SYN540405, and CGA224439, CGA300405 (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information on potential sublethal effects of trinexapac-ethyl on honeybees (e.g. effects on HPG) (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- A risk assessment for honeybees for exposure via contaminated water (surface water and puddle water) and further information to address the risk for exposure via guttation water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Further information to address the risk to honeybees for metabolites occurring in pollen and nectar (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).

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

None.

10. Concerns

10.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[13] 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.

1) The nature and magnitude of residues in primary and rotational crops and in livestock with regard to the cyclopropyl moiety of trinexapac and the behaviour of trinexapac in processed products have not been addressed. Consequently, the consumer risk assessment could not be finalised (see Section 3).
2) The consumer risk assessment from the consumption of water could not be finalised, whilst satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water, when surface water is abstracted for drinking water (see Section 4).

10.2. 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

[13] 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.

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.

3) The technical specification is not covered by the (eco)toxicological assessment (see Sections 2 and 5).

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

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

In addition to the issues indicated in the table below, the technical material specification proposed was not comparable to the material used in the (eco)toxicological testing and that was used to derive the toxicological reference values.

Table 5: Overview of concerns

Representative use		Barley (winter, spring)	Wheat (winter)
Operator risk	Risk identified		
	Assessment not finalised		
Worker risk	Risk identified		
	Assessment not finalised		
Resident/bystander risk	Risk identified		
	Assessment not finalised		
Consumer risk	Risk identified		
	Assessment not finalised	X[1,2]	X[1,2]
Risk to wild non-target terrestrial vertebrates	Risk identified		
	Assessment not finalised		
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified		
	Assessment not finalised		
Risk to aquatic organisms	Risk identified		
	Assessment not finalised		
Groundwater exposure to active substance	Legal parametric value breached		
	Assessment not finalised		
Groundwater exposure to metabolites	Legal parametric value breached[(a)]		
	Parametric value of 10 µg/L[(b)] breached		
	Assessment not finalised		

The superscript numbers relate to the numbered points indicated in Section 10.1. 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).

10.4. Issues related to the maximum residue level applications

None.

References

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Abbreviations

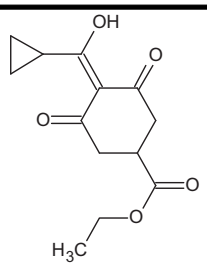
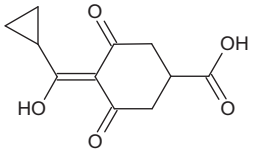
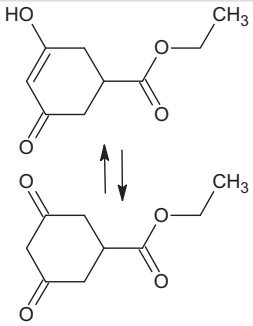
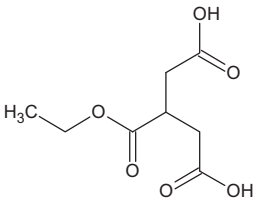
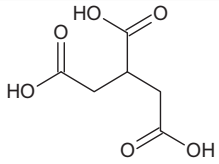
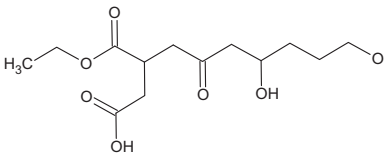
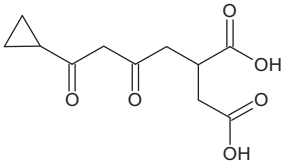
ADI	acceptable daily intake
AAOEL	acute acceptable operator exposure level
AMA	Amphibian Metamorphosis Assay

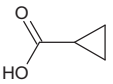
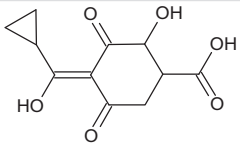
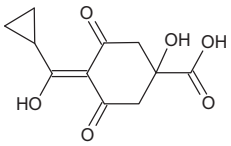
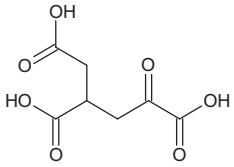
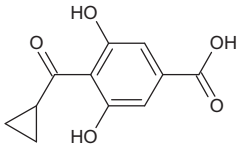
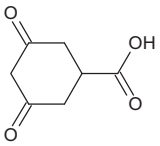
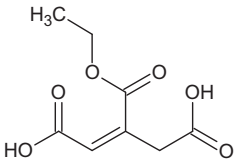
AOEL	acceptable operator exposure level
ARfD	acute reference dose
bw	body weight
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
dw	dry weight
EAS	oestrogen, androgen and steroidogenesis modalities
ECHA	European Chemicals Agency
EEC	European Economic Community
FAO	Food and Agriculture Organisation 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
HPG	hypopharygeal glands
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_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LOQ	limit of quantification
mm	millimetre (also used for mean measured concentrations)
mN	milli-Newton
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
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
QSPR	quantitative structure–property relationships
r^2	coefficient of determination
SD	standard deviation
SMILES	simplified molecular-input line-entry system
T	thyroid modality
$t_{1/2}$	half-life (define method of estimation)
TRR	total radioactive residue
WHO	World Health Organization

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

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2023.8082

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation/InChiKey[b]	Structural formula[c]
trinexapac-ethyl	ethyl (1*RS*,4*EZ*)-4-[cyclopropyl(hydroxy)methylene]-3,5-dioxocyclohexanecarboxylate O=C(OCC)C1CC(=O)/C(C(=O)C1)=C(/O)C1CC1 RVKCCVTVZORVGD-QXMHVHEDSA-N	
Trinexapac CGA179500	(1*RS*,4*EZ*)-4-[cyclopropyl(hydroxy)methylene]-3,5-dioxocyclohexanecarboxylic acid O=C1CC(CC(=O)/C1=C(/O)C2CC2)C(O)=O DFFWZNDCNBOKDI-KTKRTIGZSA-N	
CGA158377	ethyl (1*RS*)-ethyl 3-hydroxy-5-oxocyclohex-3-ene-1-carboxylate O=C(OCC)C1CC(O)=CC(=O)C1 SSXUXPNPVFUMDJ-UHFFFAOYSA-N or ethyl 3,5-dioxocyclohexane-1-carboxylate O=C(OCC)C1CC(=O)CC(=O)C1 RPRRICYOWFRORO-UHFFFAOYSA-N	
CGA300405	3-(ethoxycarbonyl)pentanedioic acid OC(=O)CC(CC(=O)O)C(=O)OCC LSGVTQNLNBOTEX-UHFFFAOYSA-N	
CGA275537 Tricarballylic acid	propane-1,2,3-tricarboxylic acid OC(=O)CC(CC(=O)O)C(=O)O KQTIIICEAUMSDG-UHFFFAOYSA-N	
M2	(3*RS*,7*RS*)-3-(ethoxycarbonyl)-7,10-dihydroxy-5-oxodecanoic acid OC(=O)CC(CC(=O)CC(O)CCCO)C(=O)OCC CMNIALBYSGFCST-UHFFFAOYSA-N	
CGA313458	(2*RS*)-2-(4-cyclopropyl-2,4-dioxobutyl)butanedioic acid O=C(CC(CC(=O)O)C(=O)O)CC(=O)C1CC1 RUOBDKPTUMNOJV-UHFFFAOYSA-N	

Code/trivial name[a]	Chemical name/SMILES notation/InChiKey[b]	Structural formula[c]
CGA224439 CPCA	cyclopropanecarboxylic acid O=C(O)C1CC1 YMGUBTXCNDTFJI-UHFFFAOYSA-N	
SYN54584 **SYN548584**	(4*E*)-4-[cyclopropyl(hydroxy)methylidene]-2-hydroxy-3,5-dioxocyclohexane-1-carboxylic acid OC(=O)C1CC(=O)C(\C(=O)C1O)=C(/O)C2CC2 GLSOUBCIOLMJGW-BQYQJAHWSA-N or 4-[cyclopropyl(hydroxy)methylidene]-1-hydroxy-3,5-dioxocyclohexane-1-carboxylic acid OC(=O)C1(O)CC(=O)/C(C(=O)C1)=C(/O)C2CC2 WKLVJNZWOHFICV-HJWRWDBZSA-N	 or 
SYN549229	4-oxobutane-1,2,4-tricarboxylic acid OC(=O)CC(CC(=O)C(=O)O)C(=O)O UMWKBSODGNZMMU-UHFFFAOYSA-N	
CGA329773	4-(cyclopropanecarbonyl)-3,5-dihydroxybenzoic acid O=C(c1c(O)cc(cc1O)C(=O)O)C2CC2 ZDXTWXUVBBGQHV-UHFFFAOYSA-N	
CGA113745	3,5-dioxocyclohexane-1-carboxylic acid O=C1CC(=O)CC(C1)C(O)=O MCGPFJGIBKPQGO-UHFFFAOYSA-N	
CGA312753 **Aconitic acid**	(2*Z*)-3-(ethoxycarbonyl)pent-2-enedioic acid OC(=O)C/C(=C/C(=O)O)C(=O)OCC FDYRUFDXTCKABB-HYXAFXHYSA-N	

(a): The compound name in bold is the name used in the conclusion.
(b): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).
(c): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).