TECHNICAL REPORT

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Outcome of the consultation with Member States, the applicant and EFSA on the pesticide risk assessment for acequinocyl in light of confirmatory data

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) was asked by the European Commission to provide scientific assistance with respect to the risk assessment for an active substance in light of confirmatory data requested following approval in accordance with Article 6(1) of Directive 91/414/EEC and Article 6(f) of Regulation (EC) No 1107/2009. In this context EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the confirmatory data and their use in the risk assessment for acequinocyl are presented. The current report summarises the outcome of the consultation process organised by the rapporteur Member State the Netherlands and presents EFSA's scientific views and conclusions on the individual comments received.

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Keywords: acequinocyl, peer review, confirmatory data, risk assessment, pesticide, acaricide

Requestor: European Commission

Question number: EFSA-Q-2017-00816

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Summary

Acequinocyl has been approved under Regulation (EC) No 1107/2009 by Commission Implementing Regulation (EU) No 496/2014. It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies by 31 August 2016 on:

(a) an analytical method for residues in body fluids and tissues;

(b) the acceptability of the long-term risk to small granivorous birds and small herbivorous and frugivorous mammals, concerning the use on apple and pear orchards;

(c) the acceptability of the long-term risk to small omnivorous and small herbivorous mammals, concerning the use on outdoor ornamentals.

In accordance with the specific provision, the applicant, Agro-Kanesho CO.LTD, submitted an updated dossier in August 2016, which was evaluated by the designated rapporteur Member State (RMS), the Netherlands, in the form of addenda to the draft assessment report. In compliance with guidance document SANCO 5634/2009-rev.6.1 , the RMS distributed the addenda to Member States, the applicant and EFSA for comments on 8 May 2017. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 30 November 2017. EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, the Netherlands, and presents EFSA's scientific views and conclusions on the individual comments received.

Acequinocyl is the ISO common name for 3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate (IUPAC). The representative formulated product for the evaluation was 'Kanemite', a suspension concentrate (SC) containing 164 g/L acequinocyl.

The representative uses evaluated comprised field and greenhouse foliar spraying to control *Tetranychus urticae* in ornamentals, and foliar spray applications to control *Panonychus ulmi* in apples and pears.

An LC-MS/MS method was submitted for the determination of acequinocyl in blood, liver and kidney, as acequinocyl-OH.

The high risk identified for herbivorous mammals remains unresolved. The risk for granivorous birds was clarified and addressed. The risk for frugivorous mammals was addressed. EFSA disagrees with the RMS that the identified risk is assumed to be low as no suitable data were available within the confirmatory dataset to support such further risk refinement.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Acequinocyl has been approved under Regulation (EC) No 1107/2009[1] by Commission Implementing Regulation (EU) No 496/2014[2]. EFSA previously finalised a Conclusion on this active substance on 19 April 2013 (EFSA, 2013).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies by 31 August 2016 on:

(a) an analytical method for residues in body fluids and tissues;

(b) the acceptability of the long-term risk to small granivorous birds and small herbivorous and frugivorous mammals, concerning the use on apple and pear orchards;

(c) the acceptability of the long-term risk to small omnivorous and small herbivorous mammals, concerning the use on outdoor ornamentals.

In accordance with the specific provision, the applicant, Agro-Kanesho CO.LTD, submitted an updated dossier in August 2016, which was evaluated by the designated rapporteur Member State (RMS), the Netherlands, in the form of addenda to the draft assessment report (Netherlands, 2017a). In compliance with guidance document SANCO 5634/2009-rev.6.1 (European Commission, 2013), the RMS distributed the addenda to Member States, the applicant and EFSA for comments on 8 May 2017. The RMS collated all comments in the format of a reporting table, which was submitted to EFSA on 30 November 2017 (Netherlands, 2017b). EFSA added its scientific views on the specific points raised during the commenting phase in column 4 of the reporting table.

The current report summarises the outcome of the consultation process organised by the RMS, the Netherlands, and presents EFSA's scientific views and conclusions on the individual comments received.

1.2. Interpretation of the Terms of Reference

On 22 December 2014 the European Commission requested EFSA to provide scientific assistance with respect to the risk assessment of confirmatory data following approval of an active substance in accordance with Article 6(1) of Directive 91/414/EEC and Article 6(f) of Regulation (EC) No 1107/2009. EFSA's scientific views on the specific points raised during the commenting phase conducted with Member States, the applicant and EFSA on the risk assessment of confirmatory data for acequinocyl are presented.

To this end, a technical report containing the finalised reporting table is being prepared by EFSA. The deadline for providing the finalised report is 28 December 2017.

On the basis of the reporting table, the European Commission may decide to further consult EFSA to conduct a full or focused peer review and to provide its conclusions on certain specific points.

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

[2] Commission Implementing Regulation (EU) No 496/2014 of 14 May 2014 approving the active substance acequinocyl, 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, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 143, 15.5.2014, p. 1–5

2. Assessment

The comments received on the pesticide risk assessment for the active substance acequinocyl in light of confirmatory data and the conclusions drawn by the EFSA are presented in the format of a reporting table.

The comments received are summarised in column 2 of the reporting table. The RMS' considerations of the comments are provided in column 3, while EFSA's scientific views and conclusions are outlined in column 4 of the table.

The finalised reporting table is provided in Appendix A of this report.

Documentation provided to EFSA

1. Netherlands, 2017a. Addenda to the assessment report on acequinocyl (B.5, B.9 MCA, B.10 MCP), confirmatory data, November 2017. Available online: www.efsa.europa.eu.

2. Netherlands, 2017b. Reporting table, comments on the pesticide risk assessment for acequinocyl in light of confirmatory data, November 2017.

References

EFSA (European Food Safety Authority), 2009. Guidance on Risk Assessment for Birds and Mammals on request from EFSA. EFSA Journal 2009;7(12):1438, 358 pp. doi:10.2903/j.efsa.2009.1438

EFSA (European Food Safety Authority), 2013. Conclusion on the peer review of the pesticide risk assessment of the active substance acequinocyl. EFSA Journal 2013,11(5):3212, 71 pp. doi:10.2903/j.efsa.2013.3212

European Commission, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1

Abbreviations

a.s.	active substance
CTGB	College voor de toelating van gewasbeschermingsmiddelen en biociden
DAR	draft assessment report
EU	European Union
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
NOAEL	no observed adverse effect level
PD	proportion of different food types
PT	proportion of diet obtained in the treated area
RMS	rapporteur Member State
SC	suspension concentrate
SFO	single first-order
TER	toxicity exposure ratio

Appendix A – Collation of comments from Member States, applicant and EFSA on the pesticide risk assessment for the active substance acequinocyl in light of confirmatory data and the conclusions drawn by EFSA on the specific points raised

Physical/Chemical Properties; Data on application and efficacy; Further Information; Methods of Analysis

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
(1)	Addendum, B.5.2.6 Study 1, p.3	EFSA: it is not clear from the description of the method how acequinocyl is transformed in acequinocyl-OH. Is it by hydrolysis with the 0.25% ammonia added?	NL: The transformation is done by acidification with 0.5% formic acid. During fortification, solutions are prepared to which formic acid is added. The ammonia is used for preparation of calibration solutions of acequinocyl-OH and during the extraction procedure. This is clarified in the revised document.	It was clarified by the applicant that the hydrolysis is done under basic conditions and considering the recoveries above 80% done by spiking with acequinocyl and quantifying as acequinocyl-OH the transformation of acequinocyl to acequinocyl-OH can be considered addressed.
(2)	Addendum, B.5.2.6 Study 1, Recovery, p.5	EFSA: it is not mentioned what was the substance used for fortification. We assume the recovery experiment was done by fortification with acequinocyl and determination of acequinocyl-OH. Is this assumption correct?	NL: Yes. This is clarified in the revised document.	According to the original study, fortification was done with acequinocyl in acetonitrile + formic acid. It was clarified by the applicant that the hydrolysis is done under basic conditions. It should be noted however, that EFSA concluded that the residue definition for urine should contain at least metabolites AKM-14 and AKM-15, and possibly AKM-05. Since no information on the content of metabolites in blood/plasma is available, the same residue definition can apply by default to blood. The analytical method for body fluids and tissues was not

				validated for the determination of metabolites AKM-14 and AKM-15.
(3)	Addendum, B.5.2.6 Study 2, p.6	EFSA: it is not clear from the description of the method how acequinocyl is transformed in acequinocyl-OH. Is it by hydrolysis with the 0.5% ammonia added?	NL: The transformation is done by acidification with 0.5% formic acid. During fortification, solutions are prepared to which formic acid is added. The ammonia is used for preparation of calibration solutions of acequinocyl-OH and during the extraction procedure. This is clarified in the revised document.	See comment (1).
(4)	Addendum, B.5.2.6 Study 1, Recovery, p.8	EFSA: it is not mentioned what was the substance used for fortification. We assume the recovery experiment was done by fortification with acequinocyl and determination of acequinocyl-OH. Is this assumption correct?	NL: Yes. This is clarified in the revised document.	See comment (2)
(5)	B.5.2.6 Study 1 & 2	DE: We agree with the conclusion that based on the validation results both methods seem acceptable. However, the suitability of the method should be further discussed since the method strongly depends on the complete degradation of acequinocyl to the OH-derivative. In this context, it should be discussed how factors such as pH of the sample, exposure to light (acequinocyl is photosensitive) and time from sample preparation to analysis can influence the conversion.	NL: Storage stability information was added to the addendum. Generally, acequinocyl is unstable once acidified. Liver extracts also proved unstable, whereas blood and kidney extracts can be stored for about a week. There is no information on sensitiveness to light, but next to a low pH, high light intensity may accelerate decomposition. Acequinocyl stocks should be refreshed daily.	See comments (2) and (3)

Ecotoxicology

No.	Column 1 Reference to addendum to assessment report	Column 2 Comments from Member States / applicant / EFSA	Column 3 Evaluation by rapporteur Member State	Column 4 EFSA's scientific views on the specific points raised in the commenting phase conducted on the RMS's assessment of confirmatory data
(1)	Addendum MCP for the evaluation of confirmatory data B.9	EFSA: agrees with the RMS evaluation of confirmatory data. The high risk identified for herbivorous mammals remains unresolved. The risk for granivorous birds was clarified and addressed. The risk for frugivorous mammals was addressed.		The high risk identified for herbivorous mammals remains unresolved. The risk for granivorous birds was clarified and addressed. The risk for frugivorous mammals was addressed.
(2)	Addendum MCA, 9.1	DE: In the overall view, the complexity assigned by the RMS to the assessment of residue decline on vertebrate food items is deemed out of proportion, taking into account the experimental constraints for such studies and the use of the data in B&M risk assessment. In particular, the FOCUS Kinetics procedures and conventions that are used in assessing degradation in soil should not be applied unchanged in an assessment of residue decline on plants.	Criteria for acceptability of fit: The procedures of FOCUS Kinetics and the statistical criteria for acceptability were derived for dissipation trials with soil, where a homogeneous distribution of the test substance in the soil (or on the soil surface) is much easier to achieve than a homogeneous distribution of residues from spraying on plants. Instead of judging trials primarily based on results of statistical tests, a discussion of, e.g., sampling procedures as a potential source of errors or uncertainties would have been more meaningful. Use of non-SFO kinetic models: The FOCUS Kinetics procedures and criteria for taking into account biphasic kinetics in the assessment were designed to ensure that long-term behaviour of residues in soil is properly/conservatively addressed in groundwater modelling. There, the	Addressed The approach from FOCUS Kinetics is considered useful. EFSA recognised that its use within the Birds and Mammals risk assessment should be further considered within the revision of EFSA (2009).

			relevant question is how long residues will be available for leaching on a timescale of years. However, such long-term behaviour is not of interest for the B&M risk assessment, because the relevant question is here what maximum peak levels or twa levels over 21 d will be reached during a spraying series, i.e. on a timescale of weeks.	
(3)	Addendum to the DAR June 2017, Volume 3, B9, B 9.1.2 Relevant ecotoxicological mammalian relevant NOAEL for acequinocyl	Applicant: With regard to the mammalian ecotoxicological relevant NOAEL, it is worrying that CTGB engages in moving the goalpost during an ongoing procedure while simultaneously contradicting itself.	For the ecotoxicological relevant NOAEL for mammals, the expert round stated a specific question - mortality in 2nd generation pups - which the applicant answered to the express satisfaction of CTGB. However, after the fact the CTGB unilaterally increased the goalpost in the EU procedure, asking additionally for an explanation of further endpoints which the expert rounds had discussed and considered as not sufficiently relevant to justify further elucidation. Worse, for the purpose of ecotoxicological evaluation, the CTGB had originally supported the higher NOEL during the expert rounds: In the pesticides peer review meeting reports from 23.04.2013 on page 5 (Expert consultation: 5.2) it is clearly stated that "the RMS agreed with the Notifiers proposed revised ecotoxicological NOEL of 55.7 mg a.s./kg bw/day instead of the lowest NOEL of 6.9 mg a.s./kg bw/day used in the first risk assessment. The RMS	Addressed The long-term endpoint agreed for the approval of the substance i.e. NOAEL of 6.9 mg/kg bw per day is considered the most appropriate endpoint for use in the wild mammal long term risk assessment.

			confirmed that they had consulted toxicology expert in evaluating the Notifiers proposal." Thus the CTGB has created conditions which denied the applicant the opportunity to formulate a strategy to address these additional questions – questions which the expert round, in consultation with ECHA (toxicological) experts, deemed as insufficiently relevant. It needs to be pointed out that without this additional argument raised by CTGB, the chronic mammal risk assessment would have to be evaluated as fully acceptable. It should also be noted that the points now raised additionally by CTGB are not new information; CTGB simply unilaterally decided to change its own interpretation of existing data. While in the national registration procedure CTGB may arguably be within its rights to deviate from the EU evaluation - even though even here it is worrying to see CTGB contradict itself compared to the position taken in the expert rounds - the purpose of the EU procedure of establishing a certain of safety at one time point, under the rules applicable at submission date - or for confirmatory data requests, the standard applicable at the time of request. Moving the goalpost, i.e. the changing the standard of evaluation

			between data request and data evaluation counter-caricatures the European evaluation system of registering substances for a certain time unless new information - not new interpretation of known data - is available.	
(4)	Addendum to the DAR June 2017, Volume 3, B9, B 9.2.2	Applicant: CTGB recalculated TERrepro = 4.1 in orchards and concludes no acceptable risk. The risk assessment contains several unrealistic worst-case assumptions.	The TER calculation conservatively considers worst-case values for PD and PT. However, there is convincing scientific evidence for voles actually not exclusively foraging on monocotyledonous grass shoots but also including dicotyledonous herbs in their diet. For example, Rinke (1991, Folia Zoologica, 40(2), 143-151) investigated the diet composition of common voles inhabiting a meadow in Germany and confirmed selective foraging behaviour with preference of dicots in spring and summer. Further studies confirm the unrealistic worst-case of the risk assessment with exclusively monocot diet (e.g. Hoogenboom et al. 1984, Oecologia 61: 18-31; Leutert 1983, Veröffentlichungen des Geobotanischen Institutes der ETH, Stiftung Rübel, Zürich. 79: 1-126). Most studies support larger quantities of dicots than monocots to be consumed by common voles. Considering a still conservative (with regard to higher residues on grass opposed to herbs) mixed diet of 2/3 grass (65%) and 1/3 herbs (35%),	The risk assessment for small herbivorous mammals was refined based on residue decline. Higher tier studies were considered not suitable to determine focal species and PT values. Therefore, based on the available data, a high risk to small herbivorous mammals is concluded for orchards and ornamentals. EFSA disagrees with the proposal of the RMS in column 3, to apply a surrogate trigger of 2 because this is not scientifically justified.

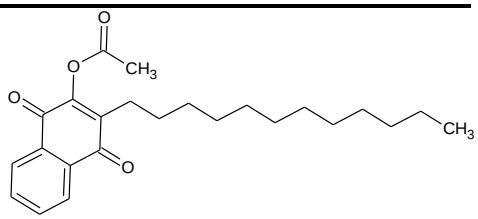
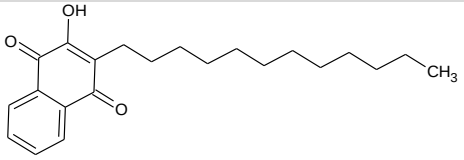
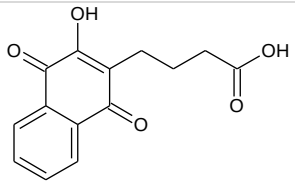
			combined with an only slightly reduced PT of 90% would result in a TER_{repro} = 5.1, indicating an acceptable risk. These refinements enhance the realism of the risk assessment without considerably reducing conservativeness and uncertainty. Finally it should be considered that the safety factor of 5 for reproductive exposure according to Directive 91/414/EEC is, amongst others, introduced to account for putative uncertainties resulting from extrapolation of toxicity data derived in laboratory studies to wild bird and mammal species. In the case of mammals, this uncertainty is negligible due to the close phylogenetic relationship of common voles to the laboratory test animals (rats, mice). Having this in mind, a safety factor of 5 most likely overestimates the risk of exposure as well as the margin of uncertainty which is probably more realistically reflected by a reduced safety factor of 2 for reproductive exposure (cf. Nolting 2010, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Bundesanzeiger. 62: 2228-2229). In conclusion, the TERrepro recalculated by CTGB is below the trigger of 5 for reproductive exposure, but it is unrealistically conservative and overestimates the risk to common voles in orchards in population level.	

			Based on more realistic estimates on PD, PT and overall toxicological uncertainty an acceptable risk has to be assumed.	
(5)	Addendum to the DAR June 2017, Volume 3, B9, B 9.2.2 Higher Tier dietary risk assessment	Applicant: CTGB recalculated TER_{repro} = 2.0 and 1.1 in ornamentals and concludes no acceptable risk. The risk assessment contains several worst-case assumptions.	The TER calculations conservatively consider worst-case values for PD and PT. Besides the generic issues detailed under No. (2) also applicable here, the relevance of the exposure scenario in ornamental fields regarding common voles is questionable. Currently, specific data to prove this are not available. The applicant is trying to close this data gap by two studies (one ongoing, one conducted by another company) in ornamental fields in the Netherlands. Existing data suggest that ornamental fields are of reduced importance for voles as foraging habitat and that the occurrence of voles is strongly influenced by surrounding habitats (e. g. Hein 2011, Bestimmung von Säugetierspezies in Zierblumenfeldern für die ökotoxikologische Risikobewertung von Pflanzenschutzmitteln, Master Thesis, Heinrich Heine Universität Düsseldorf). Particularly the structure of the landscape varies considerably across Europe and individual countries making an EU wide evaluation difficult. But it has to be assumed, that ornamental fields provide less suitable habitat for voles compared to grass strips within	See comment (4) In addition, it is noted that the data mentioned by the RMS e. g. Hein 2011, Jacob et al. 2014, Hein & Jacob 2015, were not part of the dossier.

			orchards and therefore, PT is probably even lower. Considering a similar diet composition as in orchards (see No. (1)) and a conservative but realistic PT of 60% would result in TER_{repro} = 3.8 and 2.1. This is below the trigger of 5 for reproductive exposure but exceeds the surrogate trigger of 2 which considers the reduced uncertainty due to extrapolation of laboratory tox data to wild voles. In the ctgb document "Evaluation Manual for the Authorisation of plant protection products and biocides according to Regulation (EC) No 1107/2009, EU part, Plant protection products, Chapter 7 Ecotoxicology: terrestrial; birds and mammals version 2.2, April 2017" it is suggested for agricultural crops like ornamental fields a chronic PD of 50% non-grass herbs and 50% grass should be considered which would even further increase TERrepro to 4.0 and 2.3. The data currently available rather suggest that ornamental fields are of low importance for voles on population level. Although some individuals occur in-crop, this probably is of low relevance considering their pest status in agriculture, highly fluctuating population dynamics, habitat preferences, resilience and high reproductive potential which reduce potential pesticide impact (Jacob et al. 2014, Pest Management	

			Science 70(6): 869-878). Furthermore, vole populations are able to recover rapidly even after intentional reduction e.g. through rodenticides (Hein & Jacob 2015, Wildlife Research 42(2):108-118).	

Appendix B – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
acequinocyl	3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphthyl acetate CC(=O)OC2=C(CCCCCCCCCCCC)C(=O)c1ccccc1C2=O	
Acequinocyl -OH AKM-05	2-dodecyl-3-hydroxynaphthalene-1,4-dione O=C2c1ccccc1C(=O)C(O)=C2CCCCCCCCCCCC	
AKM-14	4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)butanoic acid O=C(O)CCCC=2C(=O)c1ccccc1C(=O)C=2O	
AKM-15	6-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)hexanoic acid O=C(O)CCCCCC=2C(=O)c1ccccc1C(=O)C=2O