Modification of the existing maximum residue level for acequinocyl in sweet peppers/bell peppers

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Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant Agro-Kanesho submitted a request to the competent national authority in Germany to modify the existing maximum residue level (MRL) for the active substance acequinocyl in sweet peppers/bell peppers. The data submitted in support of the request were found to be sufficient to derive MRL proposal for peppers. Adequate analytical methods for enforcement are available to control the residues of acequinocyl in peppers at the validated limit of quantification (LOQ) of 0.01 mg/kg. Based on the risk assessment results, EFSA concluded that the short-term and long-term intake of residues resulting from the use of acequinocyl according to the reported agricultural practice is unlikely to present a risk to consumer health.

Keywords: acequinocyl, peppers, pesticide, MRL, consumer risk assessment

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Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, Agro-Kanesho submitted an application to the competent national authority in Germany (evaluating Member State, EMS) to modify the existing maximum residue levels (MRLs) for the active substance acequinocyl in sweet peppers/bell peppers. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the European Food Safety Authority (EFSA) on 29 June 2021. To accommodate for the intended use of acequinocyl, the EMS proposed to raise the existing MRL from the limit of quantification (LOQ) of 0.01 to 0.3 mg/kg.

EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation. EFSA identified points which needed further clarification, which were requested from the EMS. On 6 December 2021 the EMS submitted a revised evaluation report, which replaced the previously submitted report.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC, the data evaluated under previous MRL assessments including the review of the existing MRLs for acequinocyl and the additional data provided by the EMS in the framework of this application, the following conclusions are derived.

The metabolism of acequinocyl following foliar and/or soil treatment was investigated in crops belonging to the group of fruit crops. In investigated crops, the metabolic pathway was seen to be similar and proceeds through the hydrolysis of the acetic acid ester to the metabolite acequinocyl-OH (named as R1 in the peer review), followed by the opening of the naphthalenedione ring leading to the metabolite AKM-18 and further hydrolysis of the dodecyl aliphatic chain, resulting in the formation of phthalic acid. Based on the conclusion on the peer review of acequinocyl, acequinocyl-OH and AKM-18 were considered of a similar toxicity as the parent and unlikely to be genotoxic.

Studies investigating the nature or magnitude of acequinocyl in rotational crops are not required, since acequinocyl exhibits low persistence in soil.

Based on the metabolic pattern identified in metabolism studies, the residue definitions for raw agricultural commodities were proposed as ‘acequinocyl’ for enforcement and risk assessment during the EU peer review and the MRL review. EFSA concluded that for the crops assessed in this application, metabolism of acequinocyl in primary crops, has been sufficiently addressed and that the previously derived residue definitions are applicable.

For processed commodities, the MRL review proposed tentative residue definitions as ‘acequinocyl and acequinocyl-OH, expressed as acequinocyl’ for enforcement and risk assessment. In the framework of the present application, the applicant submitted a new standard hydrolysis study with acequinocyl radiolabelled in the phenyl ring to investigate the effect of processing on the nature of residues of acequinocyl. Due to the very low water solubility of the active substance, residues showed high affinity with the test vessels and the lids. Nevertheless, the indicative findings show that acequinocyl was the predominant compound after all hydrolysis tests and is likely to partially degrade to acequinocyl-OH (named as R1 in the peer review of acequinocyl) and AKM-18 under conditions representative to baking, brewing, boiling and sterilisation. These compounds were also observed during metabolism in primary crops. Therefore, the new hydrolysis study submitted within the present application, although presenting some deficiencies, does support the tentative residue definition derived in the MRL review. Nevertheless, the general data gap regarding the nature of residues in processed commodities should still be assessed, either in the framework of the confirmatory data for MRL review or during the renewal of the active substance, considering the deficiencies observed in the hydrolysis studies.

Sufficiently validated analytical methods based on HPLC-MS/MS are available to quantify residues in peppers according to the enforcement residue definition. The methods enable quantification of residues at or above the LOQ of 0.01 mg/kg.

The available residue trials are sufficient to derive an MRL proposal of 0.3 mg/kg for sweet peppers/bell peppers.

Specific studies investigating the magnitude of acequinocyl residues in processed peppers were not submitted. However, considering the results of the hydrolysis study submitted, the available toxicological data of parent acequinocyl and its metabolites, the lack of consumption data on processed peppers, and the large margin of safety with regard to the consumer dietary exposure to acequinocyl, such data are not deemed necessary for the present application.

Residues of acequinocyl in commodities of animal origin were not assessed, since peppers are normally not fed to livestock.
The toxicological profile of acequinocyl was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.023 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.08 mg/kg bw.

The consumer risk assessment was performed with revision 3.1 of the EFSA Pesticide Residues Intake Model (PRIMo). The short-term exposure assessment was performed for peppers and calculations were based on the highest residue (HR) derived from supervised field trials. The short-term exposure amounted to 11.2% of the ARfD. With regard to long-term exposure, a comprehensive assessment was performed in the framework of the MRL review, taking into account the existing uses at EU level. EFSA updated the calculations with the relevant median residue (STMR) value derived from the supervised residue trials submitted in support of this MRL application. The highest estimated long-term dietary intake was 8% of the ADI (Dutch toddler diet). The highest contribution of residues expected in peppers to the overall long-term exposure was 0.2% of the ADI (GEMS/Food G15 diet).

EFSA concluded, even considering existing uncertainties, that the proposed use of acequinocyl on sweet peppers/bell peppers is acceptable and would not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a risk to consumers’ health.

EFSA proposes to amend the existing MRL as reported in the summary table below.

Full details of all end points and the consumer risk assessment can be found in Appendices B–C.

| Code(a) | Commodity          | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|--------|--------------------|-------------------------|-------------------------|-----------------------|
| 0231020 | Sweet peppers/ bell peppers | 0.01*                  | 0.3                     | The submitted data are sufficient to derive an MRL proposal for the indoor use. Risk for consumers unlikely. |

MRL: maximum residue level; NEU: northern Europe; SEU: southern Europe; GAP: Good Agricultural Practice.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).

(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
(F): Fat soluble.
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Assessment

The European Food Safety Authority (EFSA) received an application to modify the existing maximum residue level (MRL) for the active substance acequinocyl in sweet peppers/bell peppers. The detailed description of the intended indoor use of acequinocyl in Germany, which is the basis for the current MRL application, is reported in Appendix A.

Acequinocyl is the ISO common name for 3-dodecyl-1,4-dihydro-1,4-dioxo-2-naphtyl acetate (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Acequinocyl was evaluated in the framework of Directive 91/414/EEC in conjunction with Regulation (EU) No 396/2005 with the Netherlands designated as the rapporteur Member State (RMS) for the representative use as field and greenhouse foliar applications on ornamentals, apples and pears. The draft assessment report (DAR) prepared by the RMS has been peer reviewed by EFSA (2013). Acequinocyl was approved for the use as an acaricide on 1 September 2014. The renewal of the approval, which is due to expire in November 2024 has not yet been initiated.

The European Union (EU) MRLs for acequinocyl are established in Annex III of Regulation (EC) No 396/2005. Since the EU pesticides peer review EFSA has issued a number of reasoned opinions on the modification of MRLs for acequinocyl and proposals from these reasoned opinions have been considered in the MRL legislation. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has been recently finalised (EFSA, 2020), but the proposed modifications have not yet been implemented in the EU MRL legislation.

In accordance with Article 6 of Regulation (EC) No 396/2005, Agro-Kanesho on 15 September 2020 submitted an application to the competent national authority in Germany (evaluating Member State, EMS) to modify the existing MRL for the active substance acequinocyl in sweet peppers/bell peppers. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to EFSA on 29 June 2021. To accommodate for the intended use of acequinocyl, the EMS proposed to raise the existing MRL from the LOQ of 0.01 to 0.3 mg/kg. EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation. EFSA identified points which needed further clarification, which were requested from the EMS. On 6 December 2021, the EMS submitted a revised evaluation report (Germany, 2021), which replaced the previously submitted evaluation report.

EFSA based its assessment on the evaluation report submitted by the EMS (Germany, 2021), the DAR and its addenda (Netherlands, 2005,2013) prepared under Council Directive 91/414/EEC, the Commission review report on acequinocyl (European Commission, 2014), the conclusion on the peer review of the pesticide risk assessment of the active substance acequinocyl (EFSA, 2013), as well as the conclusions from the reasoned opinion on the MRL review according to Article 12 of Regulation No 396/2005 (MRL review) (EFSA, 2020).

For this application, the data requirements established in Regulation (EU) No 544/2011 and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a-g,2000,2010a,b,2017; OECD, 2011). The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/2011.

1 Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1-32.
2 Commission Regulation (EU) No 188/2011 of 25 February 2011 laying down detailed rules for the implementation of Council Directive 91/414/EEC as regards the procedure for the assessment of active substances which were not on the market 2 years after the date of notification of that Directive. OJ L 53, 26.2.2011, p. 51–55.
3 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 L143, 15.5.2014, p. 1–5.
4 Regulation (EC) No 396/2005 of the 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.
5 For an overview of all MRL Regulations on this active substance, please consult: https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/active-substances/?event-search.as
6 Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ L 155, 11.6.2011, p. 1-66.
7 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.
A selected list of end points of the studies assessed by EFSA in the framework of this MRL application including the end points of relevant studies assessed previously, is presented in Appendix B.

The evaluation report submitted by the EMS (Germany, 2021) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available as background documents to this reasoned opinion.

1. **Residues in plants**

1.1. **Nature of residues and methods of analysis in plants**

1.1.1. **Nature of residues in primary crops**

The metabolism of acequinocyl was investigated in fruit crops, following foliar (apples, aubergines and oranges) and soil (aubergines) treatment (Netherlands, 2005), and assessed in the framework of the EU pesticides peer review (EFSA, 2013) and the MRL review (EFSA, 2020). In the studies conducted with apples and aubergines (both foliar and soil), acequinocyl was radiolabelled in the phenyl ring or the dodecyl chain of the molecule, while in oranges, it was labelled only in the phenyl ring. Results from trials were comparable.

In investigated crops, the metabolic pathway was seen to be similar and proceeds through the hydrolysis of the acetic acid ester to the metabolite acequinocyl-OH (named as R1 in the peer review), followed by the opening of the naphthalenedione ring leading to the metabolite AKM-18 and further hydrolysis of the dodecyl aliphatic chain, resulting in the formation of phthalic acid (EFSA, 2013).

Acequinocyl was the major component identified in the total radioactive residues (TRR) of all the studies, accounting for 28% (0.06 mg eq/kg) to 41% TRR (0.11 mg eq/kg) in apples and oranges 30 days after treatment (DAT), and for 55% TRR (0.01 mg eq/kg) in aubergines, 14 DAT. The other metabolites identified, namely acequinocyl-OH, AKM-18 and phthalic acid represented less than 0.05 mg eq/kg or 10% TRR. In leaves, at harvest, acequinocyl was also the most prominent component identified, representing up to 58% TRR (1.14 mg eq/kg) (EFSA, 2020).

For the intended use on peppers, EFSA concludes that the metabolism of acequinocyl is sufficiently elucidated and no additional investigations are necessary.

1.1.2. **Nature of residues in rotational crops**

Peppers can be grown in crop rotation. However, the field DT90 reported in the soil degradation studies evaluated in the framework of the peer review was 21 and 24 h for parent acequinocyl and metabolite acequinocyl-OH, respectively. For metabolite, AKM-18 only laboratory data were available, indicating a DT90 of 12 days (EFSA, 2013). Therefore, studies investigating the nature of acequinocyl in rotational crops are not required.

1.1.3. **Nature of residues in processed commodities**

Studies investigating the nature of residues under standard processing conditions (i.e. pasteurisation, boiling and sterilisation) were not available for the assessment by the EU pesticides peer review nor by the MRL review. Consequently, EFSA identified a data gap for standard hydrolysis studies during the MRL review (EFSA, 2020). In the absence of such studies, the MRL review used the results of processing trials on citrus fruits (mass balance study; production of juice, marmalade and canned fruits) to tentatively estimate the effects of processing on acequinocyl residues. Results indicated that the metabolite acequinocyl-OH was present after processing of citrus fruits, and this metabolite was included, on a provisional basis, in the residue definition for processed commodities (EFSA, 2020).

It has to be noted that acequinocyl is characterised by a very low water solubility (i.e. 0.007 mg/L at 25°C; EFSA, 2013). According to the OECD guideline on the nature of the pesticide residues in processed commodities, hydrolysis studies are not required for substances with a water solubility of < 0.01 mg/L (OECD, 2007). However, in the framework of the present application, the applicant submitted a new standard hydrolysis study (Germany, 2021) and made an attempt to elucidate the fate of acequinocyl under representative hydrolytic conditions. In this study, acequinocyl was only radiolabelled in the phenyl ring. In all tests representative of the standard hydrolysis conditions, the total recovery, when summing fractions recovered from the buffer solution the test vessel and the lid,
was above 90% of the applied radioactivity (AR). Significant part of the AR was adhering to the lid of the test vessel after hydrolysis (8.75–29.5% of AR), while part of it was recovered from the test vessels (0–16.2% of AR) after different hydrolysis tests (see details in Appendix B.1.1.1). Residues remaining on the lid extract were generally not analysed (except in pasteurisation assay). Residues remaining on the test vessel were generally not analysed (except in sterilisation assay). Acequinocyl was the predominant compound in all hydrolysis tests. From the results there are indications, similarly to plant metabolism studies (see Section 1.1.1), that acequinocyl degrades to acequinocyl-OH through hydrolysis of the acetic acid ester, and that AKM-18 is formed after the opening of the naphthalenedione ring. Both compounds were found at above 10% of AR after applying processing conditions representative of baking, brewing, boiling, and sterilisation. Other minor degradation products (AKM-08, AKM-14, AKM-15) were identified at lower portions below 5% of AR.

Upon EFSA's request, applicant argued that a hydrolysis study with a second radiolabelling, as normally recommended by the OECD Guideline (OECD, 2007), is not necessary. A cleavage in the molecule of acequinocyl was not observed in the study and no other breakdown products would be expected in case a second labelling position in the aliphatic carbon chain (as observed in the metabolism study performed on apples and aubergines) would be used. The RMS supported this argumentation (Germany, 2021).

In addition, the toxicity of metabolites acequinocyl-OH (R1) and AKM-18, found in the present hydrolysis tests and in primary crops, was assessed during the EU pesticides peer review (EFSA, 2013) and these compounds were characterised as unlikely to be genotoxic. These metabolites were also present in the rat metabolism and considered to be of a similar toxicity as the parent compound.

EFSA is of the opinion that the available data are sufficient, in the context of the present application, to assess the intended use on sweet peppers. The general question whether the available evidence is sufficient to address the data gap identified in the MRL review is still open and should be assessed in the framework of the confirmatory data process or in the framework of the renewal of the active substance, considering the deficiencies reported on the hydrolysis studies. Furthermore, in view of the future renewal of the approval of acequinocyl, a new assessment of this section will be performed including a re-assessment of the toxicity of the parent metabolites based on up-to-date criteria. Therefore, the conclusions reported in this reasoned opinion might need to be reconsidered.

1.1.4. Methods of analysis in plants

The availability of analytical enforcement methods for the determination of acequinocyl residues in plant commodities was investigated in the EU pesticides peer review (EFSA, 2013) and in the MRL review (EFSA, 2020).

Overall, a hyphenated analytical method based on high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) was validated for the determination of parent acequinocyl and metabolite acequinocyl-OH in high acid and high water content commodities, with an LOQ of 0.01 mg/kg, for each analyte (EFSA, 2013). Additionally, an HPLC-MS/MS method for parent acequinocyl in high acid and dry commodities was made available in the MRL review (EFSA, 2020) and the reported LOQ was 0.01 mg/kg. For the determination of parent acequinocyl and metabolite acequinocyl-OH in hops, a validated HPLC-MS/MS method is available with an LOQ of 0.1 mg/kg for each analyte (EFSA, 2020).

Additionally, in the framework of the MRL review, EU Reference Laboratories for Pesticides Residues (EURL) provided validation results on QuEChERS multi-residue method using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) with an LOQ of 0.1 mg/kg in high water, high acid and high oil content commodities and an LOQ of 0.01 mg/kg for dry commodities for the enforcement of parent acequinocyl in routine analysis. The validation failed at 0.01 mg/kg for high water, high acid and high oil content commodities. According to EURLs, metabolite acequinocyl-OH can be monitored in routine analysis in high water and high acid content commodities, as well as dry commodities at the LOQ of 0.01 mg/kg. According to EURLs, analytical standards for both, parent acequinocyl and metabolite acequinocyl-OH are commercially available (EURL, 2018).

In conclusion, sufficiently validated analytical methods exist for the determination of acequinocyl residues in high water content (relevant for the crop under consideration) at the LOQ of 0.01 mg/kg.

1.1.5. Storage stability of residues in plants

The storage stability of parent acequinocyl and its metabolite acequinocyl-OH in high water content commodities, which is relevant for the peppers under consideration, was investigated separately for
both compounds in the framework of the EU pesticides peer review demonstrating that each compound is stable for at least 18 months when stored at \(-18^\circ\)C (EFSA, 2013). Further details of available storage stability studies with acequinocyl are reported in the Appendix B.1.1.2.

1.1.6. Proposed residue definitions

Based on the metabolic pattern identified in the metabolism studies, the toxicological significance of acequinocyl and its metabolites and the capabilities of enforcement analytical methods, the following residue definitions were proposed by the EU pesticides peer review (EFSA, 2013) and confirmed in the MRL review (EFSA, 2020):

- residue definition for risk assessment (raw agricultural commodity (RAC)): acequinocyl
- residue definition for enforcement (RAC): acequinocyl

The enforcement and risk assessment residue definitions are limited to fruits and fruiting vegetables and applicable to hops (EFSA, 2020).

The residue definition for enforcement set in Regulation (EC) No 396/2005 is identical with the above-mentioned enforcement residue definition.

For processed commodities, a data gap for a study investigating the nature of acequinocyl residues under standard processing conditions was identified during the MRL review. The new hydrolysis study submitted within the present application indicates that acequinocyl is the predominant compound after hydrolysis, and partially degrades mainly to acequinocyl-OH and AKM-18. Therefore, despite the deficiencies highlighted regarding the submitted study, the indicative findings do support the tentative residue definition derived in the MRL review. A study with a second radiolabelling might be useful to fully depict the possible degradation of the side chain during hydrolysis conditions and to confirm the available results. Therefore, the general data gap regarding the nature of residues in processed commodities should still be assessed either in the framework of the confirmatory data for MRL review or in the renewal of the active substance, and the residue definition derived for processed commodities should still be considered tentative.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the intended indoor use of acequinocyl on peppers in Germany, the applicant submitted 8 indoor residue trials on peppers, performed in Germany during growth season 2019/2020. All trials were conducted in different greenhouses, in distinct locations, with a minimum distance of 140 km and, thus, all trials were considered as sufficiently independent. Spraying volume of the formulated product was adjusted to canopy height of the pepper plants, to comply with the indented GAP. Four trials were designed as a harvest trial and four as decline trials. A decline in residues over time was generally observed in pepper fruits.

The samples were analysed for acequinocyl, included in the residue definitions for enforcement and risk assessment. According to the assessment of the EMS, the analytical method used was sufficiently validated and fit for purpose. The samples of the residue trials were stored under conditions for which integrity of the samples has been demonstrated (Germany, 2021).

An MRL proposal of 0.3 mg/kg as well as risk assessment values for sweet peppers/bell peppers were derived (see Section 1.2.4).

1.2.2. Magnitude of residues in rotational crops

There are no studies investigating the magnitude of residues in rotational crops. Nevertheless, based on the very low persistence exhibited by acequinocyl and metabolites in the field soil degradation studies (DT$_{90} < 100$ days), residue levels in rotational crops are not expected to exceed 0.01 mg/kg.

1.2.3. Magnitude of residues in processed commodities

Specific processing studies for peppers were not submitted in the framework of the present assessment. However, considering the results of the hydrolysis study submitted, the available toxicological data of parent acequinocyl and its metabolites, the lack of consumption data on processed peppers, and the large margin of safety for peppers with regard to the consumer dietary...
exposure to acequinocyl (see Section 3), such data are not deemed necessary for the present application.

If processing factors are to be required by risk managers, e.g. for enforcement purposes, additional processing studies with peppers would be needed analysing for acequinocyl and its metabolite acequinocyl-OH, in line with the proposed residue definition for processed commodities. Furthermore, if processed trials were to be performed in future, it would be preferable to also investigate the possible presence of metabolite AKM-18 as uncertainty remains to its possible presence in processed commodities.

It is noted that a study examining the magnitude of residues in processed tomatoes (juice, puree, and canned tomatoes) was submitted in the framework of the present application. Processing factors (PFs) were calculated based on the tentative residue definition for processed commodities. However, due to the lack of storage stability data in examined processed commodities, and the significant differences (above 50%) in calculated PF between trials, robust processing factors could not be derived and were not used for consumer risk assessment.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive an MRL proposal as well as risk assessment values for sweet peppers/bell peppers. In Section 3 EFSA assessed whether residues on this commodity resulting from the intended use are likely to pose a consumer health risk.

2. Residues in livestock

Not relevant, as peppers are not used for feed purposes.

3. Consumer risk assessment

EFSA performed a dietary risk assessment using revision 3.1 of the EFSA PRIMo (EFSA, 2018, 2019). This exposure assessment model contains food consumption data for different sub-groups of the EU population and allows the acute and chronic exposure assessment to be performed in accordance with the internationally agreed methodology for pesticide residues (FAO, 2016).

The toxicological reference values for acequinocyl used in the risk assessment (i.e. acute reference dose (ARfD) 0.08 mg/kg body weight (bw) and acceptable daily intake (ADI) 0.023 mg/kg bw per day) were derived in the framework of the EU pesticides peer review (European Commission, 2014).

Short-term (acute) dietary risk assessment

The short-term exposure assessment was performed for peppers assessed in this application. The calculations were based on the highest residue (HR) derived from supervised field trials on peppers. The short-term exposure amounted to 11.2% of the ARfD.

Long-term (chronic) dietary risk assessment

In the framework of the MRL review a comprehensive long-term exposure assessment was performed, taking into account the existing uses at EU level (EFSA, 2020). EFSA updated the calculations with the relevant median residue (STMR) value derived from the supervised residue trials submitted in support of this MRL application. The input values used in the exposure calculations are summarised in Appendix D.1. The highest estimated long-term dietary intake was 8% of the ADI (Dutch toddler diet). The highest calculated contribution of residues expected in peppers to the overall long-term exposure was 0.2% of the ADI for the GEMS/Food G15 diet.

Although uncertainties remain due to the data gaps identified (in particular on the nature of residues in processed commodities) in the review of existing MRLs (EFSA, 2020), this indicative exposure calculation did not indicate a risk to consumer’s health. Based on these calculations, EFSA concluded that the proposed use of acequinocyl on peppers is acceptable with regard to consumer exposure.

For further details on the exposure calculations, a screenshot of the Report sheet of the PRIMo is presented in Appendix C.

4. Conclusion and Recommendations

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for sweet peppers/bell peppers.
Considering the results of the hydrolysis study submitted (with only one radiolabelling on the phenyl ring), the current endpoints regarding the toxicity of the metabolites and the large margin of safety for peppers with regard to the consumer dietary exposure to acequinocyl, EFSA concluded that the proposed use of acequinocyl on peppers will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a risk to consumers’ health.

It is highlighted that the general question whether the available evidence is sufficient to address the data gap identified in the MRL review on the lack of hydrolysis study has not be addressed in the present opinion. It should be assessed either in the framework of a confirmatory data process or in the framework of the renewal of the active substance, considering the deficiencies observed on the hydrolysis studies and reported in the present opinion.

The MRL recommendations are summarised in Appendix B.4.

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Abbreviations

a.s. active substance
ADI acceptable daily intake
AR applied radioactivity
ARfD acute reference dose
BBCH growth stages of mono- and dicotyledonous plants
bw body weight
CF conversion factor for enforcement to risk assessment residue definition
CXL Codex maximum residue limit
DAR draft assessment report
DAT days after treatment
DT₉₀ period required for 90% dissipation (define method of estimation)
EMS evaluating Member State
eq residue expressed as a.s. equivalent
EUURL EU Reference Laboratory (former Community Reference Laboratory (CRL))
FAO Food and Agriculture Organization of the United Nations
GAP Good Agricultural Practice
HPLC–MS/MS high-performance liquid chromatography with tandem mass spectrometry
HR highest residue
IEDI international estimated daily intake
IESTI international estimated short-term intake
ILV independent laboratory validation
ISO International Organisation for Standardisation
IUPAC International Union of Pure and Applied Chemistry
LC–MS/MS liquid chromatography with tandem mass spectrometry
LOQ limit of quantification
MRL maximum residue level
MS Member States
NEU northern Europe
OECD Organisation for Economic Co-operation and Development
PBI plant back interval
PF processing factor
PHI preharvest interval
PRIMo (EFSA) Pesticide Residues Intake Model
QuEChERS Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RA risk assessment
RAC raw agricultural commodity
RD residue definition
RMS rapporteur Member State
SANCO Directorate-General for Health and Consumers
SC suspension concentrate
Modification of the existing maximum residue level for acequinocyl in sweet peppers/bell peppers

SEU  southern Europe
STMR  supervised trials median residue
TMDI  theoretical maximum daily intake
TRR  total radioactive residue
WHO  World Health Organization
## Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs

| Crop and/or situation | NEU, SEU, MS or country | Pest(s) or Group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days)(d) | Remarks |
|-----------------------|-------------------------|-------------------------------------|-------------|-------------|-------------------------------|---------------|---------|
| Sweet peppers/bell peppers | DE | Spider mites | SC 150 g/L Foliar treatment - broadcast spraying | At infestation 2 10 days | 15.6 900 140.7 g a.s./ha | 3 | Canopy height 50–125 cm |
| | | | | | 15.6 1,200 187.50 g a.s./ha | | Canopy height > 125 cm |

MRL: maximum residue level; GAP: Good Agricultural Practice; NEU: northern European Union; SEU: southern European Union; MS: Member State; a.s.: active substance; SC: suspension concentrate.

(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).

(b): CropLife International Technical Monograph no 2, 7th Edition. Revised March 2017. Catalogue of pesticide formulation types and international coding system.

(c): Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including, where relevant, information on season at time of application.

(d): PHI: minimum preharvest interval.
Appendix B – List of end points

B.1. Residues in plants

B.1.1. Nature of residues and methods of analysis in plants

B.1.1.1. Metabolism studies, methods of analysis and residue definitions in plants

| Primary crops (available studies) | Crop groups | Crop(s) | Application(s) | Sampling (DAT) | Comment/Source |
|-----------------------------------|-------------|---------|----------------|----------------|---------------|
| Fruit crops                       |             |         |                |                |               |
|                                   |             | Apples  | Foliar: 1 × 750 g a.s./ha | 0, 14, 21, 30 | Radiolabelled active substance: 14C-(U)-phenyl- or 14C-dodecyl-acequinocyl (EFSA, 2013) |
|                                   |             |         |                |                |               |
|                                   |             |         | Soil: 1 × 600 g a.s./ha; Foliar: 1 × 600 g a.s./ha | 0, 7, 14 | Radiolabelled active substance: 14C-(U)-phenyl- or 14C-dodecyl-acequinocyl (EFSA, 2013) |
|                                   |             |         |                |                |               |
|                                   |             |         | Foliar: 1 × 1,050 g a.s./ha | 0, 14, 21, 30 | Radiolabelled active substance: 14C-(U)-phenyl acequinocyl (EFSA, 2013) |
| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) | Comment/Source |
|                                   |             |         |                |            |               |
| Root/tuber crops                  |             |         |                |            | Not available, not required. |
| Leafy crops                       |             |         |                |            | Not available, not required. |
| Cereal (small grain)              |             |         |                |            | Not available, not required. |
| other                             |             |         |                |            | Not available, not required. |
| Processed commodities (hydrolysis study) | Conditions | Stable? |                |            | Comment/Source |
|                                   | Pasteurisation (20 min, 90°C, pH 4) | Yes |                |            | Radiolabelled active substance: 14C-(U)-phenyl acequinocyl (Germany, 2021) Recovery in buffer solution: 74.9% AR
  - Acequinocyl: 67.2% AR
  - Acequinocyl-OH: 2.4% AR
  - AKM-18: 3.9% AR
  - AKM-08: 1.4% AR
Recovery in lid extract: 19% AR
  - Acequinocyl: 19% AR
Recovery in test vessel: 3.7% AR
  - Residues not analysed further. |
|                                   | Baking, brewing and boiling (60 min, 100°C, pH 5) | No |                |            | Radiolabelled active substance: 14C-(U)-phenyl acequinocyl (Germany, 2021) |
| Sterilisation (20 min, 120°C, pH 6) | No |
|----------------------------------|----|
| Radiolabelled active substance: $^{14}$C-(U)-phenyl acequinocyl (Germany, 2021) | |
| Recovery in buffer solution: 67.1% AR | |
| • Acequinocyl: 48.4% AR | |
| • Acequinocyl-OH: 14.8% AR | |
| • AKM-18: 3.8% AR | |
| Recovery in lid extract: 8.8% AR | |
| • Residues not analysed further. | |
| Recovery in test vessel: 16.2% AR | |
| • Acequinocyl: 2.2% AR | |
| • Acequinocyl-OH: 0% AR | |
| • AKM-18: 8.6% AR | |
| • AKM-14: 4.6% AR | |
| • AKM-15: 0.8% AR | |
### Stability of residues in plants

| Plant product (available studies) | Category | Commodity | T (°C) | Stability period | Compounds covered | Comment/ Source |
|----------------------------------|----------|-----------|--------|-----------------|-------------------|----------------|
|                                  |          |           | Value  | Unit |                  |                  |                |
| High water content               | Apples   | –18       | 18     | Months | Acequinocyl      | EFSA (2013)      |
|                                  |          | –18       | 18     | Months | Acequinocyl-OH   |                  |
| High acid content                | Oranges  | –18       | 5      | Months | Acequinocyl      | EFSA (2020)      |
|                                  |          | –18       | 5      | Months | Acequinocyl-OH   |                  |
| Processed products               | Orange, juice | –18 | 3 | Months | Acequinocyl |                  |
|                                  | Orange, oil | –18 | 3 | Months | Acequinocyl-OH |                  |
|                                  | Orange, dried pulp | –18 | 3 | Months | Acequinocyl-OH |                  |

DAT: days after treatment; a.s.: active substance; PBI: plant-back interval; AR: applied radioactivity; LOQ: limit of quantification; HPLC-MS/MS: high performance liquid chromatography coupled to tandem mass spectrometry; ILV: independent laboratory validation; QuEChERS: Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method).
B.1.2. Magnitude of residues in plants

B.1.2.1. Summary of residues data from the supervised residue trials

| Commodity                  | Region/Indoor<sup>a</sup> | Residue levels observed in the supervised residue trials (mg/kg) | Comments/Source                                                                 | Calculated MRL (mg/kg) | HR<sup>b</sup> (mg/kg) | STMR<sup>c</sup> (mg/kg) |
|----------------------------|---------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------|------------------------|--------------------------|
| Sweet peppers/Bell peppers| EU                        | 0.018; 0.038; 0.071; 0.082; 0.086; 0.11; 0.12; 0.15             | Indoor residue trials on peppers compliant with GAP. Application rate varies according to plant height as specified in the GAP description. MRL<sub>OECD</sub> = 0.26 | **0.3**                | 0.15                   | 0.084                    |

MRL: maximum residue level; GAP: Good Agricultural Practice.

(a): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, EU: indoor EU trials or Country code: if non-EU trials.

(b): Highest residue. The highest residue for risk assessment refers to the whole commodity and not to the edible portion.

(c): Supervised trials median residue. The median residue for risk assessment refers to the whole commodity and not to the edible portion.
B.1.2.2. Residues in rotational crops

Residues in rotational and succeeding crops expected based on confined rotational crop study?

| Not triggered | No study available and not required (low persistence in soil for acequinocyl and metabolites) (EFSA, 2013, 2020) |
|----------------|--------------------------------------------------------------------------------------------------|

Residues in rotational and succeeding crops expected based on field rotational crop study?

| Not triggered | No study available and not required |
|----------------|------------------------------------|

B.1.2.3. Processing factors

Processing studies relevant to the intended use on peppers were not submitted in the framework of the present MRL application.8

| Processed commodity | Number of valid studies(a) | Processing Factor (PF) | CF P(c) | Comment/Source |
|---------------------|---------------------------|-----------------------|---------|---------------|
|                     |                           | Individual values(b)  | Median PF |               |
| RD for enforcement and risk assessment (RAC): acequinocyl | | | | |
| RD for enforcement and risk assessment (processed commodities): acequinocyl and acequinocyl-OH, expressed as acequinocyl | | | | |
| Tomatoes, juice 2 | 0.87; 1.54 | 1.2 | 1 | Indicative(d) (Germany, 2021) |
| Tomatoes, puree 2 | 1.55; 5.52 | 3.54 | 1 | Indicative(d) (Germany, 2021) |
| Tomatoes, canned 2 | 0.05; 0.15 | 0.10 | 1 | Indicative(d) (Germany, 2021) |

(a): Studies with residues in the RAC at or close to the LOQ were disregarded (unless concentration may occur).
(b): Samples were analysed for acequinocyl, acequinocyl-OH, and phthalic acid. Phthalic acid was always below the LOQ. Processing factors were calculated according to the proposed residue definition for processed commodities ‘acequinocyl and acequinocyl-OH, expressed as acequinocyl’.
(c): Conversion factor for risk assessment in the processed commodity; median of the individual conversion factors for each processing residues trial.
(d): An indicative PF is derived, as the difference of two processing factors is greater than 50%. An additional trial would in principle be required. Moreover, storage stability is not proven for residues in processed commodities. In addition, the current RD for processed commodities is tentative.

B.2. Residues in livestock

Not relevant as peppers are not used for feed purposes.

B.3. Consumer risk assessment

| ARFD | 0.08 mg/kg bw (European Commission, 2014) |
| Highest IESTI, according to EFSA PRIMO | Peppers: 11.2% of ARFD |
| Assumptions made for the calculations | The calculation is based on the highest residue level (HR) expected in peppers as derived in the supervised residue trials. Calculations were performed with PRIMO revision 3.1. |

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8 A new study on the processing of tomatoes was submitted in the present application and assessed. Indicative processing factors are presented in the table below. EFSA calculated processing factors based on the proposed residue definition for processed commodities (EFSA, 2020).
### B.4. Recommended MRLs

| Code<sup>(a)</sup> | Commodity                  | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification                                                                 |
|-------------------|---------------------------|-------------------------|-------------------------|--------------------------------------------------------------------------------------|
| 0231020           | Sweet peppers/bell peppers | 0.01*                   | 0.3                     | The submitted data are sufficient to derive an MRL proposal for the indoor use. Risk for consumers unlikely. |

**Enforcement residue definition:** Acequinocyl (F)

ADIs: maximum residue level; NEU: northern Europe; SEU: southern Europe; GAP: Good Agricultural Practice.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).

<sup>(a)</sup>: Commodity code number according to Annex I of Regulation (EC) No 396/2005.

<sup>(F)</sup>: Fat soluble.

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ARD: acute reference dose; bw: body weight; ESTI: estimated short-term intake; PRIMO: EFSA Pesticide Residues Intake Model; HR: highest residue; ADI: acceptable daily intake; IEDI: international estimated daily intake; MRL: maximum residue level; STMR: supervised trials median residue.

**Modification of the existing maximum residue level for acequinocyl in sweet peppers/bell peppers**

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Appendix C – Pesticide Residue Intake Model (PRIMo)

| Input values | Details – acute risk assessment | Details – chronic risk assessment | Supplementary results – chronic risk assessment |
|--------------|--------------------------------|---------------------------------|-----------------------------------------------|
| Acequinocyl (F) |                                |                                 |                                               |
| LOQs (mg/kg) range from: 0.01 to: 0.05 |                                 |                                 |                                               |
| Details – chronic risk |                                 |                                 |                                               |
| ADI (mg/kg bw per day): 0.08 |                                 |                                 |                                               |
| ARfD (mg/kg bw): 0.01 |                                 |                                 |                                               |
| Details – acute risk |                                 |                                 |                                               |
| Source of ADI: EC |                                 |                                 |                                               |
| Year of evaluation: 2014 |                                 |                                 |                                               |
| Comments: Refined calculation mode |                                 |                                 |                                               |

**Chronic risk assessment: JMPR methodology (IEDI/TMDI)**

| Commodities | MS Diet | Highest contributor to | (% of ADI) | 2nd contributor to | (% of ADI) | 3rd contributor to | (% of ADI) |
|--------------|---------|------------------------|------------|--------------------|------------|--------------------|------------|
|          |         | (µg/kg bw per day)     |            | (µg/kg bw per day) |            | (µg/kg bw per day) |            |
| Table grapes | Netherlands toddler | 8% | 1.76 | 3% | 1.0% | 1% |
| Milk: Cattle | Germany child | 6% | 1.32 | 2% | 1.0% | 0.9% |
| Table grapes | Germany child | 4% | 0.90 | 1% | 1% | 0.7% |
| Milk: Cattle | United Kingdom general | 3% | 0.78 | 1.0% | 0.4% | 0.4% |
| Table grapes | France general | 3% | 0.76 | 2% | 0.8% | 0.2% |
| Milk: Cattle | Portugal general | 3% | 0.76 | 0.7% | 0.4% | 0.3% |
| Tomatoes | Germany child | 3% | 0.72 | 0.6% | 0.6% | 0.2% |
| Milk: Cattle | Germany child | 2% | 0.69 | 0.6% | 0.4% | 0.2% |
| Apples | France general | 2% | 0.67 | 0.6% | 0.6% | 0.2% |
| Milk: Cattle | France general | 2% | 0.66 | 0.6% | 0.6% | 0.2% |

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Acequinocyl (F) is unlikely to present a public health concern.

DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.
| Commodity                  | MRL/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI | Commodity                  | MRL/ADI (mg/kg) | Exposure (µg/kg bw) | Highest % of ARfD/ADI |
|---------------------------|-----------------|---------------------|------------------------|---------------------------|-----------------|---------------------|------------------------|
| Table grapes              | 0.8/0.45        | 33                   | 19%                    | Table grapes              | 0.8/0.45        | 15                  | 41%                    |
| Pears                     | 0.4/0.22        | 31                   | 13%                    | Wine grapes               | 0.8/0.45        | 11                  | 38%                    |
| Sweet peppers/bell peppers| 0.20/0.15       | 8.9                  | 8%                     | Grapes                    | 0.8/0.45        | 6.2                 | 10%                    |
| Oranges                   | 0.60/0.36       | 7.0                  | 4%                     | Quinces                   | 0.4/0.22        | 3.4                 | 8%                     |
| Peaches                   | 0.10/0.07       | 6.3                  | 3%                     | Sweet peppers/bell peppers| 0.20/0.15       | 3.0                 | 9%                     |
| Quinces                   | 0.40/0.20       | 5.4                  | 3%                     | Tomatoes                  | 0.30/0.15       | 2.1                 | 10%                    |
| Grapes                    | 0.60/0.06       | 4.6                  | 2%                     | Oranges                   | 0.60/0.06       | 1.8                 | 4%                     |
| Wine grapes               | 0.40/0.20       | 4.2                  | 2%                     | Mandarins                 | 0.60/0.06       | 1.5                 | 3%                     |
| Mandarins                 | 0.60/0.06       | 3.0                  | 2%                     | Peaches                   | 0.60/0.06       | 1.2                 | 6%                     |
| Pears                     | 0.40/0.20       | 3.1                  | 2%                     | Cucumbers                 | 0.30/0.15       | 1.1                 | 10%                    |
| Sweet peppers/bell peppers| 0.30/0.15       | 2.6                  | 1%                     | Mandarins                 | 0.30/0.15       | 1.1                 | 10%                    |
| Lemons                    | 0.60/0.06       | 2.0                  | 1%                     | Grapefruits               | 0.60/0.06       | 1.1                 | 1%                     |
| Tomatoes/sauce/puree       | 0.30/0.36       | 3.4                  | 5%                     | Wine grapes/wine          | 0.80/0.45       | 4.3                 | 4%                     |
| Oranges/juice             | 0.60/0.06       | 3.1                  | 4%                     | Tomatoes/sauce/puree       | 0.30/0.36       | 2.9                 | 3%                     |
| Apples/juice              | 0.40/0.05       | 2.4                  | 2%                     | Grapefruits               | 0.60/0.06       | 0.90                | 0.8%                   |
| Peaches                   | 0.10/0.07       | 1.7                  | 1%                     | Courgettes/boiled         | 0.20/0.04       | 0.91                | 0.3%                   |
| Apples/juice              | 0.40/0.05       | 1.5                  | 0.6%                   | Grapefruits               | 0.60/0.06       | 0.08                | 0.1%                   |
| Courgettes/boiled         | 0.30/0.15       | 0.8                  | 0.3%                   | Melon/nектар              | 0.80/0.01       | 0.08                | 0.1%                   |
| Courgettes/boiled         | 0.30/0.15       | 0.6                  | 0.2%                   | Watermelon                | 0.80/0.01       | 0.07                | 0.1%                   |
| Peaches                   | 0.60/0.01       | 0.29                 | 0.2%                   | Courgettes/boiled         | 0.80/0.01       | 0.13                | 0.1%                   |
| Watermelon                | 0.40/0.05       | 0.16                 | 0.00%                  | Grapes                    | 0.80/0.01       | 0.09                | 0.0%                   |
| Cucumbers                 | 0.60/0.01       | 0.19                 | 0.2%                   | Peaches                   | 0.60/0.01       | 0.06                | 0.0%                   |
| Peaches                   | 0.60/0.01       | 0.16                 | 0.2%                   | Watermelon                | 0.60/0.01       | 0.05                | 0.0%                   |
| Watermelon                | 0.60/0.01       | 0.16                 | 0.2%                   | Courgettes/boiled         | 0.80/0.01       | 0.05                | 0.0%                   |
| Cucumbers                 | 0.60/0.01       | 0.16                 | 0.2%                   | Peaches                   | 0.60/0.01       | 0.05                | 0.0%                   |
| Quinces/jam               | 0.60/0.01       | 0.16                 | 0.2%                   | Watermelon                | 0.80/0.01       | 0.05                | 0.0%                   |
| Quinces/jam               | 0.60/0.01       | 0.16                 | 0.2%                   | Courgettes/boiled         | 0.80/0.01       | 0.05                | 0.0%                   |

**Results for children**

No exceedance of the toxicological reference value was identified for any unprocessed commodity.

A short-term intake of residues of Acequinocyl (F) is unlikely to present a public health risk.

**Results for adults**

For processed commodities, no exceedance of the ARfD/ADI was identified.

The calculation is based on the large portion of the most critical consumer group.

**Conclusion:**

No exceedance of the toxicological reference value was identified for any unprocessed commodity. A short-term intake of residues of Acequinocyl (F) is unlikely to present a public health risk. For processed commodities, no exceedance of the ARfD/ADI was identified.
Appendix D – Input values for the exposure calculations

D.1. Consumer risk assessment

| Commodity                                      | Existing/Proposed MRL (mg/kg) | Source            | Chronic risk assessment | Acute risk assessment |
|------------------------------------------------|-------------------------------|-------------------|-------------------------|-----------------------|
|                                                 |                               |                   | Input value (mg/kg)     | Input value (mg/kg)   |
|                                                 |                               |                   | Comment                 | Comment               |
| Risk assessment residue definition: Acequinocyl (F) |                               |                   |                         |                       |
| Sweet peppers/bell peppers                     | 0.3                           | Intended use      | 0.084                   | ST-MR-RAC             |
|                                                |                               |                   |                         | 0.15                  | HR-RAC                |
| Other commodities of plant and animal origin    | EFSA (2020)                   |                   |                         |                       |

STMR-RAC: supervised trials median residue in raw agricultural commodity; HR-RAC: highest residue in raw agricultural commodity.
### Appendix E – Used compound codes

| Code/trivial name(a) | IUPAC name/SMILES notation/InChIKey(b) | Structural formula(c) |
|----------------------|----------------------------------------|-----------------------|
| Acequinocyl          | 3-dodecyl-1,4-dioxo-1,4-dihydro-2-naphthyl acetate  
                      CC(=O)OC1=C(CCCCCCCCCCCCC)C(=O)  
c2cccc2C1=O  
QDRXWCAYUNHOGA-UHFFFAOYSA-N | ![Structural formula](image1.png) |
| **Acequinocyl-OH**   | 2-dodecyl-3-hydroxynaphthalene-1,4-dione  
                      O=C1c2cccc2C(=O)C(=O)CCcccccccccc  
KUUFMNYPXOKFD-UHFFFAOYSA-N | ![Structural formula](image2.png) |
| **R1** **AKM-05**    |                                         |                       |
| AKM-18               | 2-(2-oxotetradecanoyl)benzoic acid  
                      OC(=O)c1ccccc1C(=O)CCCCCCCCCC  
JPCMTIJCXDBNGK-UHFFFAOYSA-N | ![Structural formula](image3.png) |
| **AKM-15**           | 6-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)hexanoic acid  
                      O = C(O)CCCCC=1C(=O)c2cccc2C(=O)C=1O  
CKKAFDDCQLAJJO-UHFFFAOYSA-N | ![Structural formula](image4.png) |
| **AKM-08**           | 2-hydroxy-3-(2-oxododecyl)naphthalene-1,4-dione  
                      CCCCCCCCCC(=O)CC=1C(=O)c2cccc2C(=O)  
C=1O  
LYNMHBROTMBUMY-UHFFFAOYSA-N | ![Structural formula](image5.png) |
| Code/trivial name\(^{(a)}\) | IUPAC name/SMILES notation/InChiKey\(^{(b)}\)                                                                 | Structural formula\(^{(c)}\)                        |
|--------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|
| AKM-14                   | 4-(3-hydroxy-1,4-dioxo-1,4-dihyronaphthalen-2-yl)butanoic acid  
                           | PDXHGIGCHBPKKD-UHFFFAOYSA-N  
                           | O = C(O)CCCC=1C(=O)c2cccccc2C(=O)C=1O                          |
| Phthalic acid            | benzene-1,2-dicarboxylic acid  
                           | OC(=O)c1cccccc1C(=O)O  
                           | XNGIFLGASWRNHJ-UHFFFAOYSA-N                                     |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key. 
(a): The metabolite name in bold is the name used in the conclusion.  
(b): ACD/Name 2021.1.3 ACD/Labs 2021.1.3 (File Version N15E41, Build 123232, 7 July 2021).  
(c): ACD/ChemSketch 2021.1.3 ACD/Labs 2021.1.3 (File Version C25H41, Build 123835, 28 August 2021).