Modification of the existing maximum residue levels for prohexadione in various oilseeds

European Food Safety Authority (EFSA),
Alba Brancato, Daniela Brocca, Luis Carrasco Cabrera, Chloe De Lentdecker, Zoltan Erdos, Lucien Ferreira, Luna Greco, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Christopher Lythgo, Paula Medina, Ileana Miron, Tunde Molnar, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Alois Stanek, Juergen Sturma, Jose Tarazona, Anne Theobald, Benedicte Vagenende and Laura Villamar-Bouza

Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant BASF SE submitted a request to the competent national authority in France to modify the existing maximum residue levels (MRL) for the active substance prohexadione in linseeds, poppy seeds, sunflower seeds, rape seeds, mustard seeds and gold of pleasure seeds. The data submitted in support of the request were found to be sufficient to derive MRL proposals for all oilseeds under consideration. Adequate analytical methods for enforcement are available to control the residues of prohexadione in commodities under consideration at the validated limit of quantification (LOQ) of 0.01 mg/kg. Based on the risk assessment results, EFSA concluded that the proposed use of prohexadione-calcium on oilseeds under consideration will not result in a consumer exposure exceeding the toxicological reference value and therefore is unlikely to pose a risk to consumers’ health. The reliable end points, appropriate for use in regulatory risk assessment are presented.

© 2018 European Food Safety Authority. EFSA Journal published by John Wiley and Sons Ltd on behalf of European Food Safety Authority.

Keywords: prohexadione, oilseed rape, sunflower seeds, pesticide, MRL, consumer risk assessment

Requestor: European Commission
Question number: EFSA-Q-2017-00687
Correspondence: pesticides.mrl@efsa.europa.eu
Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, BASF SE submitted an application to the competent national authority in France (evaluating Member State (EMS)) to modify the existing maximum residue levels (MRLs) for the active substance prohexadione in linseeds, poppy seeds, sunflower seeds, rape seeds, mustard seeds and gold of pleasure seeds. France 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 2 October 2017. To accommodate for the intended uses of prohexadione, the EMS proposed to raise the existing MRLs from the limit of quantification (LOQ) 0.01 to 0.06 mg/kg for linseed, poppy seed, mustard seeds, gold of pleasure seeds and sunflower seeds and to 0.015 mg/kg for rapeseeds.

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 May 2018, the EMS submitted a revised evaluation report, which replaced the previously submitted evaluation report.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC and Commission Regulation (EC) No 737/2007, the data evaluated under previous MRL assessments and Article 12 MRL review and the additional data provided by the EMS in the framework of this application, the following conclusions are derived.

The metabolism of prohexadione following foliar application was investigated in fruit crops, cereals/grasses and pulses/oilseeds, and the peer review concluded that parent prohexadione is the main residue in primary crops.

Studies investigating the effect of processing on the nature and the magnitude of prohexadione have not been submitted and are not required, as the total theoretical maximum daily intake (TMDI) is below the trigger value of 10% of the acceptable daily intake (ADI) and the residues in raw oilseeds are below 0.1 mg/kg.

Occurrence of prohexadione residues in rotational crops was considered in the European Union (EU) pesticides peer review where it was concluded that significant residues in rotational crops are not expected, according to results of rotational crop metabolism studies and the rate of degradation of prohexadione in soil. These conclusions also apply to the intended Good Agricultural Practices (GAPs) on oilseeds in the framework of this application.

Based on the metabolic pattern identified in metabolism studies and the toxicological significance of metabolites, the residue definitions for plant products were proposed as prohexadione and its salts, expressed as prohexadione-calcium. These residue definitions are applicable to primary and rotational crops.

EFSA concluded that for the intended uses on oilseeds, metabolism of prohexadione in primary and in rotational crops is sufficiently addressed and that the residue definitions derived by the EU pesticides review are applicable.

Sufficiently validated analytical methods based on high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) are available to quantify prohexadione residues in oilseeds assessed in this application according to the enforcement residue definition. The methods enable quantification of residues at or above 0.01 mg/kg in the crops assessed (LOQ).

The available residue trials are sufficient to derive MRL proposals for all oilseeds under consideration.

Oilseeds and their by-products (meal) can be fed to livestock and therefore the impact of residues in oilseeds from the new intended uses on the existing livestock exposure was assessed. The previously calculated dietary burden in the MRL review was now recalculated according to the OECD methodology, considering livestock intake of feed products containing prohexadione residues resulting from all authorised uses, including the new intended uses on oilseeds. The use of the OECD calculator resulted in lower dietary burdens for dairy and meat ruminants and in higher dietary burdens for swine and poultry, the latter now exceeding the trigger value of 0.1 mg/kg dry matter (DM). The main contributing commodity in all livestock diets is milled wheat by-products. The new uses on oilseed do not have an impact on the existing dietary burdens. However, since the calculated dietary burdens for poultry now exceed the trigger value, the potential carry-over of prohexadione residues in the food commodities of animal origin was investigated further.

The nature of prohexadione residues in livestock has been investigated during the EU pesticides peer review in lactating goats and laying hens and the residue definition for enforcement and risk assessment was proposed as prohexadione and its salts, expressed as prohexadione-calcium.
Based on the results of the livestock metabolism studies, the EU pesticides peer review and the MRL review concluded that at the calculated dietary burdens prohexadione residues above the LOQ are not expected in ruminant matrices. Since the calculated livestock exposure is still significantly lower than the lowest dose levels in metabolism studies for which no residues above the LOQ of 0.01 mg/kg were observed, EFSA concludes that residues above the LOQ are not expected in ruminant, swine and poultry matrices.

The toxicological profile of prohexadione was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an ADI value of 0.2 mg/kg body weight (bw) per day. An ARfD was deemed unnecessary.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). The comprehensive long-term exposure assessment which was performed in the MRL review was now updated with the STMR values derived for oilseeds from the residue trials submitted in support of this MRL application and with the STMR values derived in EFSA opinions published after the MRL review. Those crops for which uses have not been reported in the MRL review were excluded from the exposure calculation. Additionally, for poultry tissues and eggs the residues at the LOQ were included in the consumer exposure calculation.

The estimated long-term dietary intake accounted for a maximum of 0.6% of the ADI (DE child diet). The contribution of residues expected in the commodities assessed in this application to the overall long-term exposure is insignificant.

EFSA concluded that the proposed use of prohexadione-calcium on oilseeds under consideration will not result in a consumer exposure exceeding the toxicological reference value and therefore is unlikely to pose a risk to consumers’ health.

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

Full details of all endpoints and the consumer risk assessment can be found in Appendices B-D.

| Code(a) | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------|-----------|------------------------|-------------------------|-----------------------|
| 0401010 | Linseeds  | 0.01*                  | 0.05                    | The submitted data are sufficient to derive MRL proposals for NEU/SEU uses. Risk for consumers unlikely |
| 0401030 | Poppy seeds | 0.01*                | 0.05                    |                       |
| 0401050 | Sunflower seeds | 0.01*               | 0.06                    |                       |
| 0401060 | Rape seeds/Canola seeds (including turnip rape seeds and radish seeds) | 0.01* | 0.015 | |
| 0401080 | Mustard seeds | 0.01*              | 0.05                    |                       |
| 0401130 | Gold of pleasure seeds | 0.01*          | 0.05                    |                       |

Enforcement residue definition: Prohexadione (prohexadione (acid) and its salts expressed as prohexadione-calcium)

MRL: maximum residue level; NEU: northern Europe; SEU: southern Europe.
*: 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.
Table of contents

Abstract ................................................................................................................................................... 1
Summary ................................................................................................................................................. 3
Assessment .............................................................................................................................................. 6
1. Residues in plants ........................................................................................................................ 7
   1.1. Nature of residues and methods of analysis in plants .............................................................. 7
       1.1.1. Nature of residues in primary crops ....................................................................................... 7
       1.1.2. Nature of residues in rotational crops ..................................................................................... 7
       1.1.3. Nature of residues in processed commodities ................................................................................. 8
       1.1.4. Methods of analysis in plants ......................................................................................................... 8
       1.1.5. Stability of residues in plants ......................................................................................................... 8
       1.1.6. Proposed residue definitions ........................................................................................................... 8
       1.2. Magnitude of residues in plants ..................................................................................................... 8
           1.2.1. Magnitude of residues in primary crops .................................................................................. 8
           1.2.2. Magnitude of residues in rotational crops ................................................................................. 9
           1.2.3. Magnitude of residues in processed commodities ....................................................................... 9
       1.2.4. Proposed MRLs ............................................................................................................................ 10
2. Residues in livestock .......................................................................................................................... 10
   2.1. Nature of residues and methods of analysis in livestock ............................................................ 10
   2.2. Magnitude of residues in livestock ................................................................................................. 11
3. Consumer risk assessment ................................................................................................................. 11
4. Conclusion and Recommendations ..................................................................................................... 11
References ............................................................................................................................................... 11
Abbreviations ........................................................................................................................................... 12
Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs .................. 14
Appendix B – List of end points .............................................................................................................. 16
Appendix C – Pesticide Residue Intake Model (PRIMo) ...................................................................... 22
Appendix D – Input values for the exposure calculations .................................................................... 24
Appendix E – Used compound codes ................................................................................................. 25
Assessment

The detailed description of the intended uses of prohexadione-calcium in oilseed rape seed, sunflower seed and minor oilseeds which are the basis for the current maximum residue level (MRL) application is reported in Appendix A.

Prohexadione is the ISO common name for 3,5-dioxo-4-propionylcyclohexanecarboxylic acid (IUPAC). In formulated products, usually the variant prohexadione-calcium is used as an active ingredient. The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Prohexadione (considered variant prohexadione-calcium) was evaluated in the framework of Directive 91/414/EEC1 with France designated as rapporteur Member State (RMS). It was included in Annex I of this Directive by Directive 2000/50/EC2 which entered into force on 1 October 2000 for use as plant growth regulator only. For the renewal of the approval of prohexadione in the framework of Regulation (EC) No 737/20073, France and Slovakia were designated as rapporteur and co-rapporteur Member States, respectively. The representative uses supported during the EU pesticides peer review for the renewal of the authorisation were foliar spraying on apples and cereals. The additional report to the draft assessment report (DAR) has been peer reviewed by the European Food Safety Authority (EFSA, 2010). The approval of the active substance under Regulation (EC) No 1107/20094 was renewed5 for a restricted use as plant growth regulator.

The EU MRLs for prohexadione are established in Annex II of Regulation (EC) No 396/20056. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) has been performed (EFSA, 2013) and the proposed modifications have been implemented in the MRL legislation. After completion of the MRL review, EFSA has issued several reasoned opinions on the modification of MRLs for prohexadione. The proposals from these reasoned opinions have been considered in recent regulation for EU MRL legislation.7,8 There are no CXLs currently set for prohexadione-calcium.

In accordance with Article 6 of Regulation (EC) No 396/2005, BASF SE submitted an application to the competent national authority in France (evaluating Member State (EMS)) to modify the existing maximum residue levels (MRLs) for the active substance prohexadione in rape seeds, sunflower seeds, linseeds, poppy seeds, mustard seeds and gold of pleasure seeds. France 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 EFSA on 2 October 2017. To accommodate for the intended uses of prohexadione, the EMS proposed to raise the existing MRLs from the limit of quantification (LOQ) to 0.06 mg/kg for linseed, poppy seed, mustard seeds, gold of pleasure seeds and sunflower seeds and to 0.015 mg/kg for rapeseeds.

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 Directive 2000/50/EC of 26 July 2000 including an active substance (prohexadione-calcium) in Annex I to Council Directive 91/414/EC concerning the placing of plant protection products on the market, OJ L 198, 4.8.2000, p. 39–40.
3 Commission Regulation (EC) No 737/2007 of 27 June 2007 on laying down the procedure for the renewal of the inclusion of a first group of active substances in Annex I to Council Directive 91/414/EC and establishing the list of those substances. OJ L 169, 29.6.2007, p. 10–18.
4 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.
5 Commission Implementing Regulation (EU) No 702/2011 of 20 July 2011 approving the active substance prohexadione, 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 190, 21.7.2011, p. 28–32.
6 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.
7 Commission Regulation (EU) 2016/1003 of 17 June 2016 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for abamectin, acequinocyl, acetamiprid, benzovindifluorpyr, bromoxynil, fludioxonil, fluopicolide, fosetyl, mequiacet, proquinazid, propamocarb, prohexadione and tebuconazole in or on certain products. OJ L 167, 24.6.2016, p. 46–103.
8 Commission Regulation (EU) 2017/171 of 30 January 2017 amending Annexes II, III and IV to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for aminopyralid, azoxystrobin, cyrantraniliprole, cyflufenamid, cyproconazole, diethofencarb, dithiocarbamates, flazopyr, flupyrad, haloxyfop, isofetamid, metalaxyl, prohexadione, propanazafop, pyrimethanil, Trichoderma atroviride strain SC1 and zoxamide in or on certain products. OJ L 30, 3.2.2017, p. 45–111.
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 25 May 2018, the EMS submitted a revised evaluation report (France, 2018), which replaced the previously submitted evaluation report.

EFSA has based its assessment on the evaluation report submitted by the EMS (France, 2018), the DAR prepared under Directive 91/414/EEC (France, 1998), the additional report (and its addenda) to the DAR prepared in the framework of Commission Regulation (EC) No 737/2007 (France, 2009a,b), the conclusion on the peer review of the pesticide risk assessment of the active substance prohexadione (variant prohexadione-calcium) (EFSA, 2010) as well as the conclusions from previous EFSA opinions on prohexadione (EFSA, 2015, 2016, 2017), including the reasoned opinion on the review of the existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2013).

For this application, the data requirements established in Regulation (EU) No 544/20119 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, 2013). 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 546/201110.

A selected list of end points of the studies assessed by EFSA in the framework of the this MRL application, review, including the end points of relevant studies assessed previously, submitted in support of the current MRL application, are presented in Appendix B.

The evaluation report submitted by the EMS (France, 2018) 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 prohexadione in primary crops belonging to the group of fruits, cereals/grass and pulses/oilseeds has been investigated in the framework of the EU pesticides peer review and the MRL review (EFSA, 2010).

In all crops investigated, only three compounds were found in amounts exceeding 10% total radioactive residue (TRR): prohexadione (peanuts), tricarballylic acid (peanut hay, hull and barley straw) and the methoxymethyl metabolite (apples). The peer review concluded that as tricarballylic acid is a ruminant metabolite of a trans-aconitic acid that is naturally occurring in grass, further toxicological assessment is not required. The methoxymethyl metabolite was identified only in apples and additional residue trials on apples performed at exaggerated application rates indicated that under practical conditions this metabolite is not present at significant levels. Thus, the peer review and the MRL review concluded that parent prohexadione is the main residue in primary crops.

For the intended use on oilseeds, the metabolic behaviour in primary crops is sufficiently addressed.

1.1.2. Nature of residues in rotational crops

Oilseeds can be grown in a crop rotation. According to the soil degradation studies assessed in the EU pesticides peer review, DT₉₀ values of prohexadione are expected to be lower than 39 days which is below the trigger value of 100 days (EFSA, 2010). According to the European guidelines, further investigation of residues in rotational crops is therefore not required (European Commission, 1997b).

Nevertheless, studies investigating the nature of prohexadione in rotational crops have been submitted for the EU pesticides peer review, which concluded that no quantifiable prohexadione residues are expected in rotational crops (EFSA, 2010).

The same conclusion is applicable for the uses on the crops under consideration.

---

9 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.
10 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.
1.1.3. Nature of residues in processed commodities

Standard hydrolysis studies investigating the stability of prohexadione under conditions representative for pasteurisation, boiling/cooking and sterilisation are not available. Considering that the total calculated theoretical maximum daily intake (TMDI) is low (less than 10% of the acceptable daily intake (ADI)) and residues in raw agricultural commodity (RAC) are below 0.1 mg/kg, such studies are currently not necessary.

1.1.4. Methods of analysis in plants

Analytical methods for the determination of prohexadione residues were assessed during the EU pesticides peer review and the MRL review, where it was concluded that the analytical method using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) is sufficiently validated for the determination of prohexadione and its salts; in plant matrices with high water content (apple), high oil content (oilseed rape), high acid content (lemon) and in high starch content commodities (cereal grain and straw) a LOQ of 0.01 mg/kg (expressed as prohexadione-calcium) can be achieved (EFSA, 2010, 2013).

The methods are sufficiently validated for the determination of prohexadione residues (expressed as prohexadione-calcium) in the oilseeds under consideration at the LOQ of 0.01 mg/kg.

1.1.5. Stability of residues in plants

The storage stability of prohexadione has been investigated in the EU pesticides peer review and in the MRL review in commodities with high water content (apples) and in high starch content commodities (grain) for 24 months. In high oil commodities (peanuts), the freezer storage stability of prohexadione has been demonstrated for 1 month (EFSA, 2010, 2013).

In the framework of the current application, the applicant submitted a new study where the storage stability of prohexadione was investigated in oilseed rape. Samples were fortified with prohexadione-calcium, equivalent to 0.1 mg/kg prohexadione and samples were stored at ≤ –18°C (France, 2018). Analysis of the samples took place at the storage intervals of 0, 91, 182 and 365 days. The study to demonstrate storage stability up to 24 months is still on-going. Based on the currently available data it can be concluded that prohexadione-calcium is stable in oilseed rape for at least 12 months when stored deep frozen.

It is noted that the study with peanuts referred to in previous EFSA assessments (EFSA, 2013) which demonstrated the freezer storage stability of prohexadione in peanuts for 1 month is of a lower validity since, according to the EMS France, it has been performed at higher storage temperatures (–5°C) than required (≤ 18°C) by the relevant guidance documents (European Commission, 1997f). The previously demonstrated storage stability of prohexadione-calcium in high oil content commodities (1 month) is thus superseded by the new data on oilseed rape.

1.1.6. Proposed residue definitions

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

- residue for risk assessment: prohexadione and its salts, expressed as prohexadione-calcium
- residue definition for enforcement: prohexadione and its salts, expressed as prohexadione-calcium

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

EFSA concludes that these residue definitions are appropriate for the current assessment and no further information is required.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

Rapeseeds, turnip rape seeds and radish seeds

In support of the intended northern Europe (NEU) and southern Europe (SEU) uses, the applicant submitted eight GAP-compliant residue trials on winter oilseed rape in support of each use. Residue
trials were performed in various EU Member States in growing seasons of 2013–2015. In all trials, two plots per trial were treated with SE formulation according to the same experimental conditions. Additionally, in four trials from NEU and in four trials from the SEU additional plot was treated with prohexadione in suspension concentrate (SC) formulation. The highest value per trial was selected for the residue data set. Residue data indicate that suspoemulsion (SE) and SC formulations result in similar residue levels in the crop. In three SEU trials, oilseed rape received two spring treatments (intervals of 21–44 days) which is not in line with the intended use pattern. However, as residues were within the same level as in GAP-compliant trials, these data were accepted.

Residues in all trials were at or below the LOQ of 0.01 mg/kg for prohexadione, resulting in values of \(\leq 0.012\) mg/kg, when recalculated to prohexadione-calcium, using the molecular weight conversion factor of 1.18.\(^{11}\)

The residue data sets from the NEU and SEU uses were of the same data population and were therefore combined to derive an MRL proposal of 0.015 mg/kg in rape seeds.

EFSA notes that radish seeds (oil radish) and turnip rape are classified under oilseed rape (Part B of Regulation (EC) No 396/2005); considering that the GAP for these minor oilseeds is comparable with rapeseed, the residue trials in rapeseed would be the most representative ones. It is therefore proposed that for these crops the MRL proposal derived of rape seeds (0.015 mg/kg) should be applied.

**Sunflower**

In support of the intended NEU and SEU uses the applicant submitted eight GAP-compliant residue trials on sunflower for each use. Residue trials were performed in various EU Member States in growing seasons of 2014–2015. The Mann-Whitney test showed that the residue populations for NEU and SEU trials belong to the same population. Thus, based on the merged NEU and SEU residue data sets, an MRL proposal of 0.06 mg/kg is derived for sunflower seeds.

Additionally, in four trials from NEU and SEU, respectively, a separate plot was treated with one application of the active substance; these data will be considered in support of the intended GAPs on minor oilseeds (see below).

**Mustard seeds, linseeds, poppy seeds and gold of pleasure**

In support of the intended NEU and SEU uses for the listed minor oilseeds, the applicant refers to residue trials performed on sunflower with one application of prohexadione (see above). These trials are acceptable and compliant with the intended GAP on minor oilseeds under consideration. The NEU and SEU trials can be merged, since they belong to the same population (Mann-Whitney test).

The EMS proposes to combine the residue data from trials with one and two applications to derive the MRL proposal for minor oilseeds, following the considerations of the EU guidance document which states that residue data from ‘any representative of the group oilseeds (except peanuts) can be extrapolated to the whole group oilseeds (except peanut)’, if the intended application is done before forming of the edible part of the treated crop (European Commission, 2017).

However, EFSA is of the opinion that since sufficient GAP-compliant residue trials with one application are available, a sufficiently robust MRL proposal can be derived for the minor oilseeds under consideration. It is noted that the MRL proposal derived from the residue trials with one treatment (0.05 mg/kg) is slightly lower than the MRL proposal derived from the wider data set, following the approach proposed by the EMS (0.06 mg/kg).

The analytical method used to analyse residue trial samples has been sufficiently validated and is considered fit for purpose (France, 2018). The residue trial samples were stored frozen for up to 367 days in case of rape seeds and for up to 338 days in case of sunflower seeds. The new storage stability study submitted by the applicant confirms the validity of residue data with regard to the storage stability.

1.2.2. Magnitude of residues in rotational crops

Not relevant.

1.2.3. Magnitude of residues in processed commodities

New studies investigating the effect of processing on the magnitude prohexadione residues in oilseeds under consideration have not been submitted. Such studies are not necessary, considering low

\(^{11}\) MW prohexadione-Ca (250.26)/MW prohexadione (212).
residues (< 0.1 mg/kg) in raw oilseeds and low consumer exposure to prohexadione residues (< 1% of the ADI).

1.2.4. Proposed MRLs

The residue data are sufficient to derive MRL proposals and risk assessment values in all crops under consideration in support of the intended SEU and NEU uses.

2. Residues in livestock

Oilseeds and their by-products (meal) can be fed to livestock and therefore the impact of residues in oilseeds from the new intended uses on the existing livestock exposure needs to be assessed.

The most recent dietary burden has been calculated in the framework of the MRL review, using the EU methodology (EFSA, 2013). The calculated dietary burdens exceeded the trigger value of 0.1 mg/kg dry matter (DM) for all livestock species, except poultry, and the main contributing commodities were wheat bran and apple pomace. The MRL review proposed setting MRLs in swine and ruminant commodities at the LOQ, based on the calculated dietary burdens and ruminant metabolism studies.

The livestock dietary burden was now recalculated according to the OECD methodology (OECD, 2013), considering livestock intake of all feed products containing prohexadione residues resulting from all authorised uses (pome fruit, peanuts, barley, oats, rye and wheat), including the new intended uses on oilseeds.

The use of the new calculator resulted in lower dietary burdens for dairy and meat ruminants and in higher dietary burdens for swine and poultry, the latter now exceeding the trigger value of 0.1 mg/kg DM. The main contributing commodity in all livestock diets is milled wheat by-products. The new uses on oilseed do not have an impact on the dietary burdens resulting from the existing uses.

However, since the calculated dietary burdens of poultry now exceed the trigger value, the potential carry-over of prohexadione residues in the food commodities of animal origin was investigated further.

2.1. Nature of residues and methods of analysis in livestock

The nature of prohexadione in livestock has been assessed in laying hen and lactating goats in the EU pesticides peer review and in the MRL review (EFSA, 2010, 2013).

Lactating goats were dosed with 0.02 or 20 mg a.s./kg body weight (bw) per day (3 and 3,000 N the calculated maximum dietary burden for dairy ruminants). Most of the administered radioactivity was excreted. Residues in milk and tissues accounted for up to 0.1% and 0.8% of the dose, respectively. Highest residue levels were found in kidney (0.01 mg eq/kg and 21 mg eq/kg for the low and high dose, respectively), residues in all other tissues and milk were less than 0.01 mg eq/kg at the low dose rate and less than 4 mg eq/kg at the high dose rate. Prohexadione was found to be the principal component of the residue in kidney accounting for 22% of the TRR; a further metabolite was found to constitute 16% of the TRR and was identified as an ethyl 4-ethoxy-3,5-dioxo-cyclohexanecarboxylate (K1902).

Laying hens were dosed with 8.4 and 33.4 mg prohexadione-calcium in a diet, corresponding to ca. 0.7 and 2.7 mg/kg bw per day (ca. 65–260 N the calculated dietary burden for poultry). The majority of the TRR was excreted and less than 0.01% of the dose was found in tissues and blood. The TRR in tissues and eggs from the low-dose group were in all samples < 0.01 mg eq/kg; from the high-dose group, the highest TRR was observed in liver (0.03 mg eq/kg), with lower levels in eggs (0.02 mg/kg) and residues ≤ 0.01 mg eq/kg in fat and muscle. The identification of residues was undertaken for the whole egg and liver. Prohexadione was identified < 0.01 mg/kg at 15% TRR in liver and 21% TRR in eggs. Due to low residues in edible tissues, the metabolic pathway was elucidated from the high-dose group non-edible tissues. In kidney, 28% TRR (0.13 mg/kg) was identified as prohexadione and 16% TRR (0.07 mg/kg) was tricarballylic acid. The results of the study indicate very little uptake of residues in tissues; the major metabolic pathway involves metabolism of prohexadione to tricarballylic acid.

The EU pesticides peer review concluded that metabolic pathways in rodents and ruminants are comparable; the findings in ruminants can therefore be extrapolated to pigs. The residue definitions for the risk assessment and monitoring for animal commodities was concluded as ‘prohexadione and its salts, expressed as prohexadione calcium’ (EFSA, 2010). Sufficiently validated analytical methods for enforcement of the proposed residue definition are available (EFSA, 2013).
2.2. Magnitude of residues in livestock

Based on the results of the livestock metabolism studies, the EU pesticides peer review and the MRL review concluded that at the calculated dietary burdens prohexadione residues above the LOQ are not expected in ruminant matrices (EFSA, 2013).

Compared to the MRL review, the dietary burdens calculated in the current assessment were lower for ruminants (0.7 N), but higher for swine (1.9 N) and poultry (1.6 N), when using the OECD calculator. Since the calculated exposure is still significantly lower than the lowest dose levels in metabolism studies for which no residues above the LOQ of 0.01 mg/kg were observed, EFSA concludes that residues above the LOQ are not expected in ruminant, swine and poultry matrices.

3. Consumer risk assessment

EFSA performed a dietary risk assessment using revision 2 of the EFSA PRIMo (EFSA, 2007). This exposure assessment model contains food consumption data for different subgroups 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 value for prohexadione-calcium used in the risk assessment (i.e. ADI value of 0.2 mg/kg bw day) was derived in the framework of the EU pesticides peer review (EFSA, 2010). An acute reference dose (ARfD) was not allocated, as not considered necessary.

In the framework of the MRL review, a comprehensive long-term exposure assessment was performed for prohexadione-calcium residues, taking into account the existing uses at EU level (EFSA, 2013). EFSA now updated the calculation with the relevant STMR values derived for oilseeds from the residue trials submitted in support of this MRL application and with the STMR values derived in EFSA opinions published after the MRL review (EFSA, 2015, 2016, 2017). Those crops for which uses have not been reported in the MRL review were excluded from the exposure calculation. Additionally, for poultry tissues and eggs the residues at the LOQ were included in the consumer exposure calculation. The input values used in the exposure calculations are summarised in Appendix D.2.

The estimated long-term dietary intake accounted for a maximum of 0.6% of the ADI (DE child diet) (see Section B.3). The contribution of residues expected in the commodities assessed in this application to the overall long-term exposure is insignificant.

EFSA concluded that the long-term intake of residues of prohexadione-calcium resulting from the existing and the intended uses on oilseeds under consideration is unlikely to present a risk to consumer health.

4. Conclusion and Recommendations

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for rape seeds, sunflower seeds, linseeds, mustard seeds, poppy seeds and gold of pleasure seeds in support of the intended European uses.

EFSA concluded that the long-term intake of residues of prohexadione-calcium resulting from the existing uses and the intended uses on oilseeds under consideration is unlikely to present a risk to consumer health.

The MRL recommendations are summarised in Appendix B.4.

References

EFSA (European Food Safety Authority), 2007. Reasoned opinion on the potential chronic and acute risk to consumers’ health arising from proposed temporary EU MRLs. EFSA Journal 2007;5(3):32r, 1141 pp. https://doi.org/10.2903/j.efsa.2007.32r

EFSA (European Food Safety Authority), 2010. Conclusion on the peer review of the pesticide risk assessment of the active substance prohexadione (considered variant prohexadione-calcium). EFSA Journal 2010;8(3):1555, 51 pp. https://doi.org/10.2903/j.efsa.2010.1555

EFSA (European Food Safety Authority), 2013. Reasoned opinion on the review of the existing maximum residue levels (MRLs) for prohexadione according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2013; 11 (4):3192, 36 pp. https://doi.org/10.2903/j.efsa.2013.3192

EFSA (European Food Safety Authority), 2015. Setting of import tolerance for prohexadione in cherries. EFSA Journal 2015;13(12):4326, 16 pp. https://doi.org/10.2903/j.efsa.2015.4326
EFSA (European Food Safety Authority), 2016. Reasoned opinion on the modification of the existing maximum residue level for prohexadione-calcium in strawberries. EFSA Journal 2016;14(7):4528, 13 pp. https://doi.org/10.2903/j.efsa.2016.4528

EFSA (European Food Safety Authority), 2017. Reasoned opinion on the modification of the existing maximum residue level for prohexadione (considered variant prohexadione-calcium) in plums. EFSA Journal 2017;15 (6):4837, 20 pp. https://doi.org/10.2903/j.efsa.2017.4837

European Commission, 1997a. Appendix A. Metabolism and distribution in plants. 7028/IV/95-rev., 22 July 1996.

European Commission, 1997b. Appendix B. General recommendations for the design, preparation and realization of residue trials. Annex 2. Classification of (minor) crops not listed in the Appendix of Council Directive 90/642/EEC. 7029/VI/95-rev. 6, 22 July 1997.

European Commission, 1997c. Appendix C. Testing of plant protection products in rotational crops. 7524/VI/95-rev. 2, 22 July 1997.

European Commission, 1997d. Appendix E. Processing studies. 7035/VI/95-rev. 5, 22 July 1997.

European Commission, 1997e. Appendix F. Metabolism and distribution in domestic animals. 7030/VI/95-rev. 3, 22 July 1997.

European Commission, 1997f. Appendix H. Storage stability of residue samples. 7032/VI/95-rev. 5, 22 July 1997. As amended by the document: classes to be used for the setting of EU pesticide maximum residue levels (MRLs). SANCO 10634/2010, finalised in the Standing Committee on the Food Chain and Animal Health at its meeting of 23–24 March 2010.

European Commission, 2000. Residue analytical methods. For pre-registration data requirement for Annex II (part A, section 4) and Annex III (part A, section 5 of Directive 91/414). SANCO/3029/99-rev. 4.

European Commission, 2010a. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010-rev. 0, Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting of 23–24 March 2010.

European Commission, 2010b. Residue analytical methods. For post-registration control. SANCO/825/00-rev. 8.1, 16 November 2010.

European Commission, 2017. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev. 10.3, 13 June 2017.

FAO (Food and Agriculture Organization of the United Nations), 2016. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed. Pesticide Residues. 3rd Edition. FAO Plant Production and Protection Paper 225, 298 pp.

France, 1998. Draft assessment report on the active substance prohexadione prepared by the rapporteur Member State France in the framework of Council Directive 91/414/EEC, May 1998.

France, 2009a. Additional report to the draft assessment report on the active substance prohexadione prepared by the rapporteur Member State France in consultation with Slovakia in the framework of Council Regulation (EC) No 737/2007, May 2009.

France, 2009b. Addendum to the Additional report to the draft assessment report on the active substance prohexadione prepared by the rapporteur Member State France in consultation with Slovakia in the framework of Council Regulation (EC) No 737/2007, October 2009.

France, 2018. Updated Evaluation report on the modification of MRLs for prohexadione-calcium in oilseed rape and sunflower. March 2018, 40 pp.

OECD (Organisation for Economic Co-operation and Development), 2011. OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues. Available online: http://www.oecd.org

OECD (Organisation for Economic Co-operation and Development), 2013. Guidance document on residues in livestock. In: Series on Pesticides No 73. ENV/JM/MONO(2013)8, 04 September 2013.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| 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 |
| DAR | draft assessment report |
| DAT | days after treatment |
| DM | dry matter |
| DT90 | period required for 90% dissipation (define method of estimation) |
| EMS | evaluating Member State |
| eq | residue expressed as a.s. equivalent |
Modification of existing MRLs for prohexadione in various oilseeds

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
ILV independent laboratory validation
ISO International Organisation for Standardisation
IUPAC International Union of Pure and Applied Chemistry
LOQ limit of quantification
MRL maximum residue level
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
RA risk assessment
RAC raw agricultural commodity
RD residue definition
RMS rapporteur Member State
SANCO Directorate-General for Health and Consumers
SC suspension concentrate
SE suspoemulsion
SEU southern Europe
SMILES simplified molecular-input line-entry system
SP water-soluble powder
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 | F G or I(1) | Pests or group of pests controlled | Preparation | Type(b) | Conc. a.s. | Method kind | Range of growth stages & season(c) | Number min-max | Interval between application (min) | Application rate per treatment | Remarks |
|-----------------------|-------------------------|------------|------------------------------------|-------------|----------|----------|------------|----------------------------------|----------------|-------------------------------|--------------------------------|---------|
| Oilseed rape, winter  | AT, BE, CZ, DE, HU, NL, PL, RO, SK, SL, UK, FR, BG, HR | NEU, SEU, I | Plant growth regulator | SC | 300 g/L | SP | BBCH 13-20 | 1 | – | – | 100–400 50 g/ha | Autumn application Can be applied in tank mix with ammonium sulfate at 1.0 kg/ha |
| Oilseed rape, winter  | AT, BE, CZ, DE, HU, NL, PL, RO, SK, SL, UK, FR, BG, HR | NEU, SEU, I | Plant growth regulator | SC | 300 g/L | SP | BBCH 13-20 | 2 | 14 | – | 100–400 25 g/ha | Autumn – split application of 2 × 0.5 L/ha Can be applied in tank mix with ammonium sulfate at 0.5 kg/ha |
| Oilseed rape, winter  | AT, BE, CZ, DE, HU, NL, PL, RO, SK, SL, UK, FR, BG, HR | NEU, SEU, I | Plant growth regulator | SC | 300 g/L | SP | BBCH 13-20 + BBCH 21-59 | 2 | Interval defined by veget. break over winter | – | 100–400 50 g/ha | Autumn and spring application Can be applied in tank mix with ammonium sulfate at 1.0 kg/ha |
| Oilseed rape, winter and summer | AT, BE, CZ, DE, HU, NL, PL, RO, SK, SL, UK, FR, BG, HR | NEU, SEU | Plant growth regulator | SC | 300 g/L | SP | BBCH 21-59 | 1 | – | – | 100–400 50 g/ha | Spring application Can be applied in tank mix with ammonium sulfate at 1.0 kg/ha |
| Oilseed rape, winter and summer | FR, BG, HR | NEU, SEU | Plant growth regulator | SC | 300 g/L | SP | BBCH 21-59 | 2 | 14 | – | 100–400 25 g/ha | Spring – split application of 2 × 0.5 L/ha Can be applied in tank mix with ammonium sulfate at 0.5 kg/ha |
| Crop and/or situation | NEU, SEU, MS or country | Pests or group of pests controlled | Preparation Type(b) | Conc. a.s. | Method kind | Range of growth stages & season(c) | Number (min-max) | Interval between application (min) | PHI (d) | Remarks |
|-----------------------|--------------------------|------------------------------------|--------------------|----------|-------------|----------------------------------|-----------------|-----------------------------------|--------|---------|
| Sunflower             | NEU, SEU, BG, CZ, HR, HU, RO, SK, SI | Plant growth regulator | SE                 | 25 g/ L  | SP          | BBCH 31-59                      | 2               | 21                                | 100-400 | 50 g/ha | Product can be applied in tank-mix with ammonium sulfate at 0.75 kg/ha or a local water conditioner of comparable activity. |
| Turnip rape, mustard seeds, linseeds, poppy seeds, gold of pleasure seeds, oil radish | NEU, SEU, AT, BE, CZ, DE, HU, NL, PL, RO, SK, SL, UK, FR, BG, HR | Plant growth regulator | SC                 | 300 g/ L | SP          | BBCH 21-59                      | 1               | -                                 | 100-400 | 25-50 g/ha | Can be applied in tank-mix with ammonium sulfate at 1.0 kg/ha (or a local water conditioner of comparable activity). Dose rate range from 0.6 to 1.0 L/ha |

NEU: northern European Union; SEU: southern European Union; MS: Member State; GAP: Good Agricultural Practice; MRL: maximum residue level; SC: suspension concentrate; SE: suspemulsion; SP: water-soluble powder.
(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).
(b): CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. 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 | Crops | Applications | Sampling (DAT) | Comment/Source |
|----------------------------------|-------------|-------|--------------|----------------|---------------|
| Fruit crops                      | Apples      | Foliar| 2 × 0.98 kg/ha | 45             | Radiolabelled active substance |
| Cereals/grass                    | Barley      | Foliar| 1 × 0.13–0.14 kg/ha | 2, 8 and 66 | (all crops): 3- or 5-14C-cyclohexenone (France, 2009a; EFSA, 2010) |
| Rice                             |             | Foliar| (a)1 × 0.03 kg/ha; (b) 1 × 0.3 kg/ha | 50 25 and 50 |           |
| Pulses/oilseeds                  | Peanut      | Foliar| 1 × 1.12 kg/ha | 0, 13 and 22 |               |

| Rotational crops (available studies) | Crop groups | Crops | Applications | PBI (DAT) | Comment/Source |
|-------------------------------------|-------------|-------|--------------|-----------|---------------|
| Root/tuber crops                    | Turnip      | Bare soil | 0.38 kg/ha | 31        | (France, 2009a; EFSA, 2010) |
| Leafy crops                         | Lettuce     | Bare soil | 0.38 kg/ha | 31        |               |
| Cereal (small grain)                | Wheat       | Bare soil | 0.38 kg/ha | 31, 121   |               |

| Processed commodities (hydrolysis study) | Conditions | Stable? | Comment/Source |
|------------------------------------------|------------|---------|----------------|
| Pasteurisation (20 min, 90°C, pH 4)      |            | Not triggered |           |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | | Not triggered |             |
| Sterilisation (20 min, 120°C, pH 6)      |            | Not triggered |               |

Can a general residue definition be proposed for primary crops? Yes

Rotational crop and primary crop metabolism similar? Yes

Residue pattern in processed commodities similar to residue pattern in raw commodities? Unknown

Plant residue definition for monitoring (RD-Mo) Prohexadione and its salts expressed as prohexadione-calcium

Plant residue definition for risk assessment (RD-RA) Prohexadione and its salts expressed as prohexadione-calcium

Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs) Matrices with high water content, high oil content, high acid content and high starch content matrices: HPLC–MS/MS, LOQ 0.01 mg/kg, expressed as prohexadione-calcium (EFSA, 2010). Independent laboratory validation (ILV) available

DAT: days after treatment; PBI: plant-back interval; ADI: acceptable daily intake; RAC: raw agricultural commodity; HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification.
# B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category       | Commodity     | T (°C) | Stability period | Compounds covered | Comment/Source |
|------------------------------------|----------------|---------------|--------|------------------|-------------------|----------------|
|                                    | High water content | Apples         | −5     | 24 Months        | Prohexadione-Ca   | EFSA (2010)     |
|                                    | High oil content   | Rape seeds     | −18    | 12 Months        | Prohexadione-Ca   | France (2018)   |
|                                    | Dry/high starch    | Wheat grain    | −20    | 24 Months        | Prohexadione-Ca   | EFSA (2010)     |
|                                    | Others            | Straw          | −20    | 24 Months        | Prohexadione-Ca   | EFSA (2010)     |
|                                    |                  | Forage         | −20    | 24 Months        | Prohexadione-Ca   | EFSA (2010)     |
### 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) |
|----------------------------------------|------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|--------------------------|--------------------------|
| Oilseed rape (incl. turnip rape seeds, radish seeds) | NEU                          | 8 × < 0.012                                                     | Residue trials on oilseed rape. Three residue trials were performed with shorter interval between treatments (spring applications), but as residues were within the same range as in compliant trials, these data were accepted. NEU and SEU residue data sets were of the same population and therefore combined to derive a MRL proposal. The calculated MRL is also applicable to turnip rape seeds and radish seeds. | **0.015**               | 0.012                    | 0.012                    |
|                                          | SEU                          | 6 × < 0.012; 2 × 0.012                                           |                                                                                                                                                                                                             |                        |                          |                          |
| Sunflower seed                          | NEU                          | < 0.012; 0.012; 0.016; 0.018; 0.021; 0.024; 0.026; 0.036        | Residue trials on sunflower compliant with the GAP (2 × 50 g a.s./ha). The MRL proposal calculated based on the merged NEU and SEU residue trials.                                                            | **0.06**               | 0.036                    | 0.02                     |
|                                          | SEU                          | 2 × < 0.012; 0.014; 0.017; 0.019; 0.021; 2 × 0.024              |                                                                                                                                                                                                             |                        |                          |                          |
| Mustard seed, linseed, poppy seed and gold of pleasure | NEU                          | Sunflower: 1 application: < 0.012; 0.012; 0.013; 0.028         | Four residue trials on sunflower compliant with the GAP (1 × 50 g a.s./ha). Since residue data sets from NEU and SEU are of a similar population, data were combined. Extrapolation to mustard seed, linseed, poppy seed and gold of pleasure. | **0.05**               | 0.028                    | 0.014                    |
|                                          | SEU                          | Sunflower: 1 application: 0.013; 0.014; 0.016; 0.018           |                                                                                                                                                                                                             |                        |                          |                          |

MRL: maximum residue level; GAP: Good Agricultural Practice.
(a): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, Indoor: 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.
(d): Supervised trials median residue according to the residue definition for monitoring.
(e): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.
B.1.2.2. Residues in rotational crops

Residues in rotational and succeeding crops expected based on confined rotational crop study?  
No

Residues in rotational and succeeding crops expected based on field rotational crop study?  
No

B.1.2.3. Processing factors

No processing studies were submitted in the framework of the present MRL application.

B.2. Residues in livestock

| Relevant groups (sub-groups) | Dietary burden expressed in | Most critical subgroup<sup>(a)</sup> | Dietary burden for existing uses | Most critical commodit<sup>(b)</sup> | Trigger exceeded (Y/N) |
|-----------------------------|-----------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------|
|                             | mg/kg bw per day Median    | Maximum                          | mg/kg DM Median                  | Maximum                          |                        |
| Cattle (all)                | 0.006                       | 0.007                            | 0.17                             | 0.18                             | Dairy cattle           | 0.18 Wheat, milled by-products | Y                      |
| Cattle (dairy only)         | 0.006                       | 0.007                            | 0.16                             | 0.17                             | Dairy cattle           | 0.17 Wheat, milled by-products | Y                      |
| Sheep (all)                 | 0.01                        | 0.01                             | 0.23                             | 0.24                             | Lamb                   | 0.24 Wheat, milled by-products | Y                      |
| Sheep (ewe only)            | 0.006                       | 0.007                            | 0.19                             | 0.21                             | Ram/Ewe               | 0.21 Wheat, milled by-products | Y                      |
| Swine (all)                 | 0.007                       | 0.007                            | 0.23                             | 0.23                             | Swine (finishing)      | 0.23 Wheat, milled by-products | Y                      |
| Poultry (all)               | 0.009                       | 0.009                            | 0.13                             | 0.13                             | Poultry layer         | 0.13 Wheat, milled by-products | Y                      |
| Poultry (layer only)        | 0.009                       | 0.009                            | 0.13                             | 0.13                             | Poultry layer         | 0.13 Wheat, milled by-products | Y                      |
| Fish                        | N/A                         |                                  |                                  |                                  |                        |                        |                        |

bw: body weight; DM: dry matter.
(a): When one group of livestock includes several subgroups (e.g. poultry ‘all’ including broiler, layer and turkey), the result of the most critical subgroup is identified from the maximum dietary burdens expressed as ‘mg/kg bw per day’.
(b): The most critical commodity is the major contributor identified from the maximum dietary burden expressed as ‘mg/kg bw per day’.
# B.2.1. Nature of residues and methods of analysis in livestock

## B.2.1.1. Metabolism studies, methods of analysis and residue definitions in livestock

| Livestock (available studies) | Animal       | Dose (mg/kg bw per day) | Duration (days) | Comment/Source                                                                                                                                 |
|-------------------------------|--------------|-------------------------|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
|                               | Laying hen   | 0.7 or 2.7 prohexadione-Ca (or 0.6 or 2.3 mg/kg bw per day prohexadione) | 5               | Hen (5 birds). Label position: 3- or 5-14C-cyclo-Hexenone (France, 2009b)                                                                        |
|                               | Lactating ruminants | 0.02 or 20 prohexadione-Ca (or 0.017 or 16.80 mg/kg bw per day prohexadione) | 10              | Goat (3 animals). Label position: 3- or 5-14C-cyclo-hexenone (France, 2009a, EFSA, 2013)                                                 |

(a): Assuming the body weight of laying hen of 1.9 kg and daily feed intake of 130 g (OECD, 2013).
(b): MW prohexadione (212)/MW prohexadione-Ca (250.26).

- **Time needed to reach a plateau concentration in milk and eggs (days)**
  - Not applicable (EFSA, 2010)

- **Metabolism in rat and ruminant similar**
  - Yes

- **Can a general residue definition be proposed for animals?**
  - Yes

- **Animal residue definition for monitoring (RD-Mo)**
  - Prohexadione and its salts expressed as prohexadione-calcium

- **Animal residue definition for risk assessment (RD-RA)**
  - Prohexadione and its salts expressed as prohexadione-calcium

- **Fat soluble residues**
  - No

- **Methods of analysis for monitoring of residues (analytical technique, matrix, LOQs)**
  - Bovine muscle, bovine liver, bovine kidney, milk, egg, fat: HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

## B.2.1.2. Stability of residues in livestock

| Animal products (available studies) | Animal | Commodity | T (°C) | Stability period | Compounds covered | Comment/Source |
|-------------------------------------|--------|-----------|--------|------------------|-------------------|----------------|
|                                     | Hen    | Liver     | −20    | 17 months        | Prohexadione-calcium | France, 2009b |
B.3. **Consumer risk assessment**

Acute exposure assessment not calculated since no ARfD has been considered necessary.

| ADI | 0.2 mg/kg bw per day (EFSA, 2010) |
| --- | ---------------------------------- |
| Highest IEDI, according to EFSA PRIMO | 0.6% ADI (DE child diet) |
| Assumptions made for the calculations | The calculation is based on the median residue levels derived for raw agricultural commodities. |
|  | The contributions of commodities where no GAP was reported in the framework of the MRL review were not included in the calculation. The residues at the LOQ of 0.01 mg/kg were considered for poultry tissues and bird’s eggs. |

ADI: acceptable daily intake; bw: body weight; IEDI: international estimated daily intake; PRIMO: (EFSA) Pesticide Residues Intake Model; GAP: good agricultural practice; MRL: maximum residue level; LOQ: limit of quantification.

B.4. **Recommended MRLs**

| Code(a) | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------|------------|------------------------|-----------------------|-----------------------|
| 0401010 | Linseeds   | 0.01*                  | 0.05                  | The submitted data are sufficient to derive MRL proposals for NEU/SEU uses. Risk for consumers unlikely |
| 0401030 | Poppy seeds | 0.01*                  | 0.05                  |                        |
| 0401050 | Sunflower seeds | 0.01*                  | 0.06                  |                        |
| 0401060 | Rape seeds/Canola seeds | 0.01*                  | 0.015                 |                        |
| 0401080 | Mustard seeds | 0.01*                  | 0.05                  |                        |
| 0401130 | Gold of pleasure seeds | 0.01*                  | 0.05                  |                        |

MRL: maximum residue level; NEU: northern Europe; SEU: southern Europe.
*: 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.

Enforcement residue definition: Prohexadione (prohexadione (acid) and its salts expressed as prohexadione-calcium)
Appendix C – Pesticide Residue Intake Model (PRIMo)

### Prohexadione-Ca

| Status of the active substance: | Included |
|-------------------------------|---------|
| Code no.                      |         |
| LOQ (mg/kg bw):               | Proposed LOQ |

| Toxicological endpoints | ADI (mg/kg bw per day): | ARfD (mg/kg bw): | Source of ADI: |
|-------------------------|-------------------------|-----------------|----------------|
|                         | 0.2                     | n.n.            | EFSA           |

| Year of evaluation: | 2010 | Year of evaluation: | 2010 |
|---------------------|------|---------------------|------|

| No. of diets exceeding ADI: | 0 – 1 |

#### Chronic risk assessment – refined calculations

| Commodity/group of commodities | 2nd contributor to MS diet (in % of ADI) | 3rd contributor to MS diet (in % of ADI) | pTMRLs at LOQ (in % of ADI) |
|-------------------------------|----------------------------------------|----------------------------------------|----------------------------|
| 0.6 DE child                  | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.5 NL child                  | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.3 DK child                  | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.3 WHO cluster diet B        | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.3 ES child                  | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.2 WHO cluster diet D        | 0.1 Wheat                              | 0.1 Wheat                              | Wheat                      |
| 0.2 FR infant                 | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 WHO cluster diet E        | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 IT kids/toddler           | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 WHO cluster diet F        | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 SE general population 90th percentile | 0.1 Wheat | 0.1 Wheat | Apple |
| 0.2 IE adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 FR toddler                | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 WHO regional European diet | 0.1 Wheat | 0.1 Wheat | Apple |
| 0.2 UK toddler                | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 PT general population     | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.2 NL general                | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 FR all population         | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 ES adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 LT adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 IT adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 UK infant                 | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 DK adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 UK vegetable              | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 UK adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 PL general population     | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |
| 0.1 FI adult                  | 0.1 Wheat                              | 0.1 Wheat                              | Apple                      |

#### Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs, were below the ADI. A long-term intake of residues of prohexadione-Ca is unlikely to present a public health concern.
### Acute risk assessment/children – refined calculations

For each commodity, the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002); for lettuce, a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would lead to an exposure equivalent to 100% of the ARfD.

| No of commodities for which ARfD/ADI is exceeded (IESTI 1): | -- | No of commodities for which ARfD/ADI is exceeded (IESTI 2): | -- | No of commodities for which ARfD/ADI is exceeded (IESTI 1): | -- | No of commodities for which ARfD/ADI is exceeded (IESTI 2): | -- |
|------------------------------------------------------------|----|------------------------------------------------------------|----|------------------------------------------------------------|----|------------------------------------------------------------|----|
| IESTI 1                                                     | *) | IESTI 2                                                     | **) | IESTI 1                                                     | *) | IESTI 2                                                     | **) |
| Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | *) | Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | **) | Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | *) | Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | **) |

### Acute risk assessment/adults/general population – refined calculations

For each commodity, the calculation is based on the highest reported MS consumption per kg bw and the corresponding unit weight from the MS with the critical consumption. If no data on the unit weight was available from that MS an average European unit weight was used for the IESTI calculation.

In the IESTI 1 calculation, the variability factors were 10, 7 or 5 (according to JMPR manual 2002); for lettuce, a variability factor of 5 was used.

In the IESTI 2 calculations, the variability factors of 10 and 7 were replaced by 5. For lettuce the calculation was performed with a variability factor of 3.

Threshold MRL is the calculated residue level which would lead to an exposure equivalent to 100% of the ARfD.

| No of commodities for which ARfD/ADI is exceeded (IESTI 1): | -- | No of commodities for which ARfD/ADI is exceeded (IESTI 2): | -- |
|------------------------------------------------------------|----|------------------------------------------------------------|----|
| IESTI 1                                                     | *) | IESTI 2                                                     | **) |
| Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | *) | Highest % of ARfD/ADI Commodities pTMRL/threshold MRL (mg/kg) | **) |

### Conclusion:

As no ARfD was considered necessary, it is concluded that the short-term intake of Prohexadione-Ca residues is unlikely to present a public health concern.
Appendix D – Input values for the exposure calculations

D.1. Livestock dietary burden calculations

| Feed commodity            | Median dietary burden | Maximum dietary burden |
|---------------------------|-----------------------|------------------------|
|                           | Input value (mg/kg)   | Comment                | Input value (mg/kg) | Comment |
| **Risk assessment residue definition:** Prohexadione and its salts expressed as prohexadione-calcium |
| Barley, oat, rye, triticale, wheat straw | 0.05 STMR (EFSA, 2013) | 0.08 HR (EFSA, 2013)  |
| Barley, oat, rye, triticale, wheat grain | 0.05 STMR (EFSA, 2013) | 0.05 STMR (EFSA, 2013) |
| Apple pomace | 0.25 STMR (0.05) (EFSA, 2013) × PF (5)(a) | 0.25 STMR (0.05) (EFSA, 2013) × PF (5)(a) |
| Dried brewer’s grain | 0.17 STMR grain (EFSA, 2013) × PF (3.3)(a) | 0.17 STMR grain (EFSA, 2013) × PF (3.3)(a) |
| **Rape seed meal** | 0.02 STMR × PF (2)(a) | 0.02 STMR × PF (2)(a) |
| Dried distiller’s grain | 0.17 STMR grain (EFSA, 2013) × PF (3.3)(a) | 0.17 STMR grain (EFSA, 2013) × PF (3.3)(a) |
| **Linseed meal** | 0.03 STMR × PF (2)(a) | 0.03 STMR × PF (2)(a) |
| **Sunflower meal** | 0.04 STMR × PF (2)(a) | 0.04 STMR × PF (2)(a) |
| Peanut meal | 0.12 STMR (EFSA, 2013) × PF (2)(a) | 0.12 STMR (EFSA, 2013) × PF (2)(a) |
| Wheat gluten meal | 0.09 STMR grain (EFSA, 2013) × PF (1.8)(a) | 0.09 STMR grain (EFSA, 2013) × PF (1.8)(a) |
| Wheat, milled by-products | 0.35 STMR grain (EFSA, 2013) × PF (7)(a) | 0.35 STMR grain (EFSA, 2013) × PF (7)(a) |

STMR: supervised trials median residue; HR: highest residue; PF: processing factor.
In bold: crops under consideration in this assessment.
(a): In the absence of processing factors supported by data, default processing factors were included in the calculation to consider the potential concentration of residues in these commodities.

D.2. Consumer risk assessment

| Commodity                                      | Input value (mg/kg) | Chronic risk assessment |
|-----------------------------------------------|---------------------|------------------------|
| **Risk assessment residue definition:** Prohexadione and its salts, expressed as prohexadione-calcium |
| Linseeds, poppy seeds, mustard seeds, gold of pleasure seeds | 0.014 STMR |
| Rape seeds | 0.012 STMR |
| Sunflower seeds | 0.02 STMR |
| Plums | 0.01 EFSA (2017) |
| Strawberries | 0.01 EFSA (2016) |
| Cherries | 0.05 EFSA (2015) |
| Poultry commodities; Birds eggs | 0.01 LOQ (dietary burden triggered under current assessment) |
| Other commodities of plant and animal origin | STMR See Table 4-1 of the EFSA reasoned opinion on the MRL review (EFSA, 2013) |

STMR: supervised trials median residue; LOQ: limit of quantification; MRL: maximum residue level.
## Appendix E – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey<sup>(a)</sup> | Structural formula<sup>(b)</sup> |
|------------------|-----------------------------------------------|---------------------------------|
| prohexadione     | 3,5-dioxo-4-propionylcyclohexanecarboxylic acid  
O=C1CC(CC<sup>(−O)</sup>C1C<sup>(−O)</sup>CC)C(O)=O  
BUCOQPHDYUOJSI-UHFFFAOYSA-N | ![Structural formula](image1.png) |
| prohexadione-calcium | calcium 3-oxido-5-oxo-4-propionylcyclohex-3-enecarboxylate  
[Ca<sup>2+</sup>.O=C1CC(CC<sup>(−O)</sup>)C1C<sup>(−O)</sup>CC)C(O)<sup>(−O)</sup>]  
QKWLAUAUGXSSE-UHFFFAOYSA-L | ![Structural formula](image2.png) |
| methoxymethyl metabolite BX-112-I5 | 3-hydroxy-4-(methoxymethyl)-5-oxocyclohex-3-ene-1-carboxylic acid  
O=C1CC(CC(O)=C1COC)C(O)=O  
ZZEHAULRTRNEQT-UHFFFAOYSA-N | ![Structural formula](image3.png) |
| KI 1902          | ethyl 4-ethoxy-3,5-dioxocyclohexane-1-carboxylate  
CCOC1C<sup>(−O)</sup>CC(CC1<sup>−O</sup>)C<sup>(−O)</sup>OCC  
UUCUESNIIUSUBIC-UHFFFAOYSA-N | ![Structural formula](image4.png) |
| tricarballylic acid | propane-1,2,3-tricarboxylic acid  
OC<sup>(−O)</sup>CC(CC<sup>(−O)</sup>O)C<sup>(−O)</sup>O  
KQTIICEAUMSDG-UHFFFAOYSA-N | ![Structural formula](image5.png) |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.  
<sup>(a)</sup>: ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).  
<sup>(b)</sup>: ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).