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Setting of maximum residue limits for propargite in citrus fruits and tea

European Food Safety Authority (EFSA)

Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the evaluating Member State (EMS) Italy received an application from Arysta LifeScience Great Britain Ltd to set maximum residue levels (MRL) for the active substance propargite in imported citrus fruits and tea. Italy 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. According to EFSA, the data are sufficient to derive a MRL proposal of 4 mg/kg for oranges only, as the extrapolation to the whole group is not supported by the EU rules. Based on the residue trials, an MRL of 50 mg/kg for tea could be derived. However, a risk manager decision is required whether the setting of a MRL of 50 mg/kg for tea is acceptable since the MRL reported to be into force in India is 10 mg/kg. Adequate analytical enforcement methods are available to control the residues of propargite on the commodities under consideration. Since the enforcement method of analysis is not enantioselective, residues are determined as the sum of any possible isomer ratio of the active substance propargite. EFSA concluded that the use of propargite on oranges and tea as reported in the countries of origin will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a consumer health risk. However, it should be noted that the risk assessment is affected by uncertainties linked to the toxicological profile and the reliability of results for some of the metabolites included in the residue definition and it is applicable to the technical propargite with the isomer ratio 99:1 under assessment.

Keywords: propargite, citrus fruits, tea, MRL application, consumer risk assessment

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Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, the evaluating Member State (EMS) Italy received an application from Arysta LifeScience Great Britain Ltd to set maximum residue levels (MRLs) for the active substance propargite in citrus fruits and tea. Italy proposed the MRL of 4 mg/kg for oranges imported from Brazil, as the extrapolation to the whole group is not supported, and of 50 mg/kg for tea imported from India. Italy 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).

EFSA based its assessment on the updated evaluation report submitted by the EMS, the draft assessment report and the additional report to the draft assessment report prepared under Directive 91/414/EEC, the Commission review report on propargite, the conclusion on the peer review of the pesticide risk assessment of the active substance propargite, the Joint Meeting on Pesticide Residues (JMPR) Evaluation report as well as the conclusion from the previous EFSA opinion on the review of the existing MRLs according to Article 12 of Regulation (EC) No 396/2005 for propargite.

The toxicological profile of propargite was assessed in the framework of the European Union (EU) pesticides peer review. Additional data were submitted with this import tolerance request which were discussed during the Experts' Teleconference 153. The data were sufficient to derive an acceptable daily intake (ADI) of 0.03 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.06 mg/kg bw for propargite. These toxicological reference values were concluded to apply also to the metabolites proposed for inclusion in the residue definition for risk assessment of citrus fruits and tea.

The metabolic pathway of propargite observed in the new metabolism studies representative for the reported uses on citrus and tea was comparable to the findings from previous studies. The residue definition for enforcement as propargite proposed during the EU pesticides peer review for fruit crops and currently set in Regulation (EC) No 396/2005 is therefore applicable to citrus and tea. For risk assessment, EFSA agreed with the proposal of the EMS to have two different residue definitions:

- Fruit crops: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, carboxy-TBPC, carboxy-TBPC-diol, carboxy-TBPC triol, expressed as propargite.
- Tea: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, HOMe-TBPC-glucoside, carboxy-TBPC-diol, expressed as propargite.

EFSA concluded that the submitted supervised residue trials were sufficient to derive a MRL proposal of 4 mg/kg on oranges, but the extrapolation to the whole group of citrus fruits is not supported. Based on the residue trials, an MRL of 50 mg/kg for tea could be derived. However, a risk manager decision is required whether the setting of a MRL of 50 mg/kg for tea is acceptable since the MRL reported to be into force in India is 10 mg/kg. It is noticed that disregarding the highest value (statistically detected as outlier) a MRL of 10 mg/kg is derived from the remaining seven trials. Adequate analytical enforcement methods are available to monitor the residues of propargite on the commodities under consideration at the validated limit of quantification (LOQ) of 0.01 mg/kg. Since the enforcement method of analysis is not enantioselective, residues are determined as the sum of any possible isomer ratio of the active substance propargite.

Studies investigating the nature of propargite residues under standard hydrolysis conditions were assessed in the framework of this import tolerance request and it was concluded that the same residue definition as for primary crops can be applied to the processed orange and tea products assessed. From the processing studies on oranges and tea provided, the following processing factors (PF) were derived, which are recommended to be included in Annex VI of Regulation (EC) No 396/2005:

– orange, (peeled) fresh juice: 0.05 – tea, brewed: 0.02

As the use of propargite is on imported crops, investigations of residues in rotational crops are not required.

The feed by-product dry pulp from imported oranges may be fed to cattle and pigs. The calculated livestock dietary burden exceeded the trigger value of 0.004 mg/kg bw. Metabolism in livestock with the active substance propargite was investigated in lactating goats. Based on the metabolism studies, it was concluded that significant residues of propargite in animal commodities are not expected, considering livestock exposure linked to the use on oranges in Brazil.

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo), taking into account the median and highest residue levels for oranges and tea derived from the residue trials submitted and the peeling factor for orange pulp. The highest calculated chronic

intake accounted for 6.3% of the ADI (IE, adult). The contribution of residues to the total consumer exposure was less than 0.2% (oranges) and 6.2% (tea) of the ADI. An acute consumer risk was not identified as well (94% and 4% of the ARfD for tea and oranges, respectively).

Based on the risk assessment results, EFSA concluded that the use of propargite on oranges and tea as authorised in the exporting countries will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a consumer health risk.

EFSA acknowledged that there are uncertainties in the risk assessment regarding:

- EFSA emphasised that there is no final FAO specification nor agreed EU specification for propargite and the name propargite may apply to several of the possible stereoisomers of the compound. EFSA considered the genotoxic potential of propargite technical material as a whole (i.e. active substance and associated impurities) since genotoxicity studies on individual impurities are not available. Therefore, the present assessment is expected to cover technical propargite as used in the studies considered in this import request and containing a *trans*:*cis* isomer ratio of 99:1.
- The toxicological profile of some of the metabolites included in the residue definition. As there are no indications that they should be of higher toxicity than the parent, overall EFSA supported the EMS' opinion to consider also this set of metabolites as covered by the parent.
- The stability of the metabolites included in the residue definition for risk assessment following processing. Although the stability of TBPC is expected to be addressed by the available hydrolysis study, a standard hydrolysis study performed with all other metabolites included in the residue definition for risk assessment was not available.
- The full reliability of the residue levels of some of the metabolites included in the residue definition for tea. Although the components containing the HOMe-TBPC and carboxy-TBPC structure showed to be stable, the stability of their respective diol conjugates in tea matrix was not addressed. Moreover, TBPC-diol was not analysed for in the residue trials and levels estimated based on the metabolism study.

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

Code[(a)]	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Propargite[(F)]				
0110020	Oranges	0.01*	4	Import tolerance supported by data. The MRL set in Brazil is 5 mg/kg Unlikely to pose a consumer health risk
0610000	Tea	0.05*	Risk manager option	Import tolerance supported by data Based on the residue trials, an MRL of 50 mg/kg for tea could be derived. However, a risk manager decision is required whether the setting of a MRL of 50 mg/kg for tea is acceptable since the MRL reported to be into force in India is 10 mg/kg. It is noticed that disregarding the highest value (statistically detected as outlier) a MRL of 10 mg/kg is derived from the remaining seven trials on tea Unlikely to pose a consumer health risk

MRL: maximum residue level.
*: 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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Background

Regulation (EC) No 396/2005[1] (hereinafter referred to as 'the Regulation') establishes the rules governing the setting of pesticide maximum residue levels (MRLs) at European Union (EU) level. Article 6 of the Regulation lays down that any party having a legitimate interest or requesting an authorisation for the use of a plant protection product in accordance with Directive 91/414/EEC[2], repealed by Regulation (EC) No 1107/2009[3], shall submit to a Member State, when appropriate, an application to set an import tolerance in accordance with the provisions of Article 7 of the Regulation.

Italy, hereafter referred to as the evaluating Member State (EMS), received from the company Arysta LifeScience Great Britain Ltd an application to set import tolerances for the active substance propargite in citrus fruits and tea. This application was notified to the European Commission and the European Food Safety Authority (EFSA) and was subsequently evaluated by the EMS in accordance with Article 8 of the Regulation.

After completion, the evaluation report was submitted to the European Commission and to EFSA on 5 February 2016. The application was included in the EFSA Register of Questions with the reference number EFSA-Q-2016-00120 and the following subject:

Propargite – Setting import tolerance of existing MRLs in citrus fruits and teas

Italy proposed to raise the existing MRLs of propargite from the limit of quantification (LOQ) of 0.01 to 4 mg/kg in oranges and from the LOQ of 0.05 to 50 mg/kg in tea.

EFSA proceeded with the assessment of the application and the evaluation report as required by Article 10 of the Regulation. EFSA identified points which needed further clarification, which were requested from the EMS. In November 2017, the EMS submitted the last revised evaluation report (Italy, 2017) which replaced the previously submitted versions.

In accordance with Article 10 of Regulation (EC) No 396/2005, EFSA shall, based on the evaluation report provided by the EMS, provide a reasoned opinion on the risks to the consumer associated with the application.

The revised evaluation report submitted by the EMS (Italy, 2017) 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.

In accordance with Article 11 of the Regulation, the reasoned opinion shall be provided as soon as possible and at the latest within 3 months (which may be extended to 6 months if more detailed evaluations need to be carried out) from the date of receipt of the application. If EFSA requests supplementary information, the time limit laid down shall be suspended until that information has been provided.

The active substance and its use pattern

The details of the Good Agricultural Practices (GAPs) for which the import tolerance was requested are given in Appendix A.

Propargite is the ISO common name for (1*RS*,2*RS*;1*RS*,2*SR*)-2-(4-*tert*-butylphenoxy)cyclohexyl prop-2-ynyl sulfite (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix B. The peer reviewed use for propargite was as acaricide.

It is noted that propargite is a mixture of two enantiomeric pairs of diastereomers. The current ISO common name does not define any specific ratio of those isomers. FAO tentative specification exists for propargite (code: AGP:CP/206), published under the old specification procedure (FAO, 1984). Since a specific ratio is not indicated, the name propargite may apply to several of the possible stereo-isomers of the compound. The experimental studies submitted in this import tolerance request, including the new genotoxicity studies, were conducted using a technical propargite with the ratio of (1*RS*,2*RS*)- and (1*RS*,2*SR*)-isomers (*trans*:*cis*) of approximately 99:1 (Italy, 2017). Therefore, the conclusion drawn up in this reasoned opinion shall be applicable to an active substance with the above isomer ratio.

Propargite was evaluated in the framework of Directive 91/414/EEC with France being the initial designated rapporteur Member State (RMS). Following the Draft Assessment Report (DAR) submission

[1] 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.

[2] 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.

[3] 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.

however, all applicants voluntarily withdrew, in accordance with Article 11e of Regulation (EC) No 1490/2002[4], their support for the inclusion of propargite in Annex I to Directive 91/414/EEC. Consequently, a first decision on non-inclusion of the active substance was published by means of Commission Decision 2008/934/EC[5], which entered into force on 31 December 2008. In accordance with Article 13 of Regulation (EC) No 33/2008[6], propargite was subject to a resubmission procedure and a second peer review was carried out by EFSA (2011) with Italy being the designated rapporteur Member State. On the basis of the initial DAR and the additional data submitted by the RMS, critical concerns were identified by EFSA with regard to the risk for consumers, operators, workers and bystanders as well as the ecotoxicological assessment. In particular, due to the lack of representativeness of the toxicity studies compared to technical specification, the setting of toxicological reference values was not achieved. Consequently, a final decision not to approve propargite under Regulation (EC) No 1107/2009, replacing Directive 91/414/EEC, was published by means of Commission Regulation (EU) 943/2011[7], which entered into force on 13 October 2011. According to this regulation, amending Commission Decision 2008/934/EC, any period of grace granted by Member States in accordance with the provisions of Article 46 of Regulation (EC) No 1107/2009 expired on 31 December 2012.

The representative uses evaluated in the first peer review were foliar spray applications on apples, grapes and tomatoes; in the second peer review process, the representative uses were limited to foliar spray applications on grapes and tomatoes.

The EU MRLs for propargite are established in Annex V of Regulation (EC) No 396/2005. Since the entry into force of the Regulation, EFSA has issued a reasoned opinion on the review of the existing MRLs for propargite according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2013). Considering that propargite was no longer approved as pesticide within the European Union and no authorised use in third countries was notified, EFSA proposed to set all MRLs of propargite at the specific LOQ or the default MRL value of 0.01 mg/kg. The proposal from this reasoned opinion has been implemented in the EU legislation by means of the Regulation (EU) No 2015/400[8].

Codex Alimentarius has established maximum residue limits (Codex maximum residue limits (CXLs)) for a range of commodities, including citrus and tea for which the CXL is set at 3 and 5 mg/kg, respectively.

For citrus, the MRL established in Brazil is 5 mg/kg.[9] For tea, according to the Indian Tea Planters' Association an MRL of 10 mg/kg is currently established in India. However, clear evidence that this value was actually established by the regulatory authority in India was not provided by the applicant.

Assessment

EFSA has based its assessment on the revised evaluation report submitted by the EMS (Italy, 2017), the draft assessment report and the additional report to the draft assessment report (France, 2007; Italy, 2010), the Commission review report on propargite (European Commission, 2011), the conclusion on the peer review of the pesticide risk assessment of the active substance propargite (EFSA, 2011), the JMPR Evaluation report (FAO, 2002) as well as the conclusions from the EFSA opinion on the review of the existing MRLs for propargite according to Article 12 of Regulation (EC) No 396/2005 (EFSA, 2013).

[4] Commission Regulation (EC) No 1490/2002 of 14 August 2002 laying down further detailed rules for the implementation of the third stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000. OJ L 224, 21.8.2002, p. 23–48.

[5] Commission Decision 2008/934/EC of 5 December 2008 concerning the non-inclusion of certain active substances in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing these substances. OJ L 333, 11.12.2008, p. 11–14.

[6] Commission Regulation (EC) No 33/2008 of 17 January 2008 laying down detailed rules for the application of Council Directive 91/414/EEC as regards a regular and an accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of that Directive but have not been included into its Annex I. OJ L 15, 18.1.2008, p. 5–12.

[7] Commission implementing Regulation (EU) No 943/2011 of 22 September 2011 concerning the non-approval of the active substance propargite, 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 Commission Decision 2008/934/EC. OJ L 246, 23.9.2011, p. 16–17.

[8] Commission Regulation (EU) 2015/400 of 25 February 2015 amending Annexes II, III and V to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for bone oil, carbon monoxide, cyprodinil, dodemorph, iprodione, metaldehyde, metazachlor, paraffin oil (CAS 64742-54-7), petroleum oils (CAS 92062-35-6) and propargite in or on certain products. OJ L 71, 14.3.2015, p. 56–113.

[9] Resolution RE No 158 of 19/1/2010, Official Journal of Brazilian Government (DOU) of 20/1/2010. Monograph P17 – Propargite.

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[10], the OECD guidance document on overview of residue chemistry studies (OECD, 2009) and the applicable guidance documents relevant for the consumer risk assessment of pesticide residues (European Commission, 2000, 2010a,b, 2013, 2017; OECD, 2011, 2013).

1. Method of analysis

1.1. Methods for enforcement of residues in food of plant origin

The MRL review confirmed that the existing gas chromatography–mass spectrometry (GC–MS) method and/or the multiresidue Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) detection were adequately validated to enforce residues of propargite at the LOQ of 0.01 mg/kg in the commodities with high water (tomato, apple), high acid (grape), high protein (dry bean) and high starch (cereals) content (EFSA, 2013).

The applicant provided validation data for the multiresidue QuEChERS method (HPLC–MS/MS) in orange and tea matrices. The method determined propargite with a LOQ of 0.01 mg/kg.

EFSA concluded that sufficiently validated analytical methods are available to monitor compliance with the proposed MRLs according to the residue definition as propargite. Since the analytical methods are not enantioselective, residues are determined as the sum of all the possible stereo-isomers of the active substance propargite.

1.2. Methods for enforcement of residues in food of animal origin

Since the setting of MRLs in products of animal origin is not required based on the reported use on oranges in Brazil, no further data are necessary in the framework of this import tolerance request.

2. Mammalian toxicology

2.1. Active substance

The toxicological profile of the **active substance** propargite was already peer reviewed by EFSA in 2011. EFSA considered a critical area of concern the lack of representativeness of the toxicity studies, in particular genotoxicity studies compared to technical specification. A data gap was identified to address the toxicological relevance of the impurities since quantitative structure–activity relationship (QSAR) raised concern regarding genotoxicity. In addition, due to the fact that propargite exerts carcinogenic potential on different organs in two strains of rats and a genotoxic mode of action could not be disregarded, no reliable reference values could be set during the peer review. The peer review considered that a new valid genotoxicity data package with the proposed specification should be made available. Therefore, the risk assessment during the peer review could not be conducted leading to a critical area of concern. Valid information addressing the behaviour of the isomers in the mammalian metabolism was also missing, as well as data on their potentially different toxicity and an analysis of the material tested in the toxicity studies with regard to different composition of isomers (EFSA, 2011).

The possible preferential metabolism/degradation of each enantiomer in mammals was not investigated in the framework of this application; however, there was no indication of preferential metabolism in crops and further data considering consumer risk assessment for the supported uses under this MRL application are not required (see Section 3).

In the framework of this application, the applicant submitted a set of new valid genotoxicity studies. In addition, the applicant provided a new *in vitro* hepatocyte comparative metabolism study in different species and strains of rats. The outcome of these new studies was discussed during experts' teleconference 153 with the EMS and Germany.

The main metabolic pathway in mammals was hydrolysis of the propynyl sulfite side-chain, subsequent oxidation and conjugation of the ter-butyl moiety, and hydroxylation of the cyclohexyl moiety. An additional pathway is metabolism of the alkyl side-chain by glutathione conjugation (EFSA, 2011).

[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.

QSAR analysis (DEREK) identified the alkyl side-chain as an alert for genotoxicity in the active substance propargite. The alkyl side chain is also present in some impurities and metabolites. The QSAR prediction raised concerns regarding the impurity profile of the technical material and its genotoxic potential (EFSA, 2011).

The new valid genotoxicity studies on propargite indicated that propargite technical material is genotoxic *in vitro* in the Mouse Lymphoma assay and negative *in vivo* in the transgenic rodent assay (TGR) using Fisher rats. Although the carcinogenic potential was observed in a different strain of rats (Wistar and CD-SD) than the one used in the *in vivo* TGR study (Fisher), the experts considered the results of the *in vitro* hepatocyte comparative metabolism study as evidence to support extrapolation between rat strains. The experts also noted that the high dose in the *in vivo* TGR is lower than the maximum dose level of the OECD guideline for the TGR assay but close to the maximum tolerable dose. A decrease of the body weight gain of 30% is reported at similar doses linked to toxicity and/or potential palatability issues observed in a short term toxicity study (5 weeks). In addition the dose regimen applied corresponds to the doses showing tumours in carcinogenicity studies. Overall, the weight of evidence for genotoxicity relied on valid and negative *in vivo* genotoxicity studies that overruled the concerns raised by QSAR analysis and results of *in vitro* test. The experts considered the propargite technical material (i.e. active substance and associated impurities) unlikely to be genotoxic.

The equivalence of toxicity studies to the previous technical material specification as proposed during the peer review (EFSA, 2011) cannot be done on the basis of available information. Therefore, from the toxicological point of view, given that the main concern was genotoxicity, the experts considered that minimum purity of propargite technical material and specification for impurities should be in line with the composition of the new genotoxicity studies (i.e. Lot LT3H20C569 in Italy, 2017). EFSA highlighted to risk managers that there is no final FAO specification nor agreed EU specification for propargite. EFSA considered the genotoxic potential of propargite technical material as a whole (i.e. active substance and associated impurities) since genotoxicity studies on individual impurities are not available.

Low acute toxicity is observed when propargite is administered by the oral route. In short-term oral studies with rats and dogs, the target organ was the jejunum in rats and the haematopoietic system in dogs. The dog was the most sensitive species. The relevant short-term oral no observed adverse effect level (NOAEL) could not be identified as the lowest dose level tested in the 1-year dog study was a lowest observed adverse effect level (LOAEL) (5 mg/kg body weight (bw) per day) (EFSA, 2011).

Long-term studies were performed with rats and mice. In rats, the target organs were the testes, haemolymphoreticular system and jejunum. In mice, the potential target organ was the spleen. Non specific effects such as reduced body weight gain (rats) and reduced food consumption (rat and mice) were also observed. No carcinogenic potential was observed in mice. However, propargite exerts carcinogenic potential on different organs in two strains of rats (Wistar and CD-SD rats). Mammary tumours were observed in Wistar rats and intestinal (mainly jejunal sarcomas) tumours were observed in both strains. Mechanism studies were performed in rats to investigate the mode of action of intestinal tumours (jejunal sarcomas): transient jejunal cell proliferation was observed after 1 week but was not confirmed later after 4 weeks and 20 months. However, a clear indication of the mechanism of action is not available and the transient cell proliferation it causes, cannot account for all observed tumours (EFSA, 2011). A genotoxic mode of action is now excluded on the basis of new valid genotoxicity studies.

The relevant long-term NOAEL is 3.46 mg/kg bw per day (long-term toxicity study in CD-SD rats) (EFSA, 2011).

Fertility and overall reproductive performance were not impaired. The parental, reproductive and offspring NOAELs are 5.1 mg/kg bw per day. In the developmental toxicity studies in rats, there was no evidence of developmental toxicity effects. In rabbits, fused sternebrae and fused skull bones occurred at doses producing also maternal toxicity (decreased body weight gain). However, it was agreed that the maternal toxicity could not be clearly linked to the developmental effects. The relevant maternal NOAELs are 18 mg/kg bw per day for the rat and 4 mg/kg bw per day for the rabbit. The relevant developmental NOAELs are 105 mg/kg bw per day for the rat and 6 mg/kg bw per day for the rabbit (EFSA, 2011).

No potential for neurotoxicity was observed in the standard toxicity studies (EFSA, 2011).

In 2011, the EFSA peer review proposed classification and labelling regarding skin sensitisation, repeated exposure toxicity and developmental toxicity in addition to harmonised classification and labelling at that time (Toxic by inhalation, irritating to skin, risk of serious damage to eyes and limited evidence of a carcinogenic effect) (CLP00, Annex VI to Regulation (EC) No 1272/2008[11]). Under this MRL application, EFSA did not reconsider the classification and labelling under the new CLP criteria and is not aware that a new CLH report had been sent to ECHA for reconsideration of classification and labelling of propargite. Under this MRL application EFSA did not consider whether propargite could be considered an endocrine disruptor nor an immunotoxic substance. Published literature has not been considered under this MRL application.

Regarding the setting of reference values the experts agreed to set the acceptable daily intake (**ADI**) of 0.03 mg kg bw per day based on the rat carcinogenicity study and supported by the dog study with an uncertainty factor (UF) of 100. Regarding the acute reference dose (**ARfD**), the EMS considered that there is no need to set an ARfD. Germany proposed to set the ARfD on the maternal NOAEL of 4 mg/kg bw per day based on developmental rabbit study if the maternal effects are observed at the beginning of the study. Otherwise, Germany would propose the offspring NOAEL of 6 mg kg bw per day as point of departure. No agreement was reached during the meeting. EFSA considered appropriate to set the ARfD on the basis of offspring NOAEL of 6 mg kg bw per day since maternal effects were not observed at the beginning of the study. The resulting ARfD is 0.06 mg/kg bw (UF of 100).

2.2. Metabolites

The experts also discussed the toxicological profile of the **metabolites** found as a residue either in crops or livestock. Although the applicant indicated during the peer review that some toxicity studies were available no toxicity studies were submitted during this MRL application. The assessment of metabolites mainly relied on consideration on the metabolic pathway in mammals and their amount found in urine. The amount found in other body fluids than urine, QSAR analysis regarding genotoxicity and comparative assessment with livestock metabolism was also considered by the EMS.

The experts agreed that at least carboxy-TBPC, carboxy-TBPC-diol and carboxy-TBPC triol are covered by parent (i.e. at least as toxic as the parent). Regarding other metabolites, i.e. TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-glucoside and HOMe-TBPC diol, the EMS considered them also covered by parent. No agreement was reached during the meeting. Germany considered that the metabolites are not major rat or mice metabolites in urine and therefore not covered. EFSA acknowledged that there are still some uncertainties regarding the toxicological profile of this set of metabolites; however, there are no indications that they should be of higher toxicity than the parent (i.e. no additional relevant functional groups are included during the metabolic pathway in these metabolites compared to parent). Overall, EFSA supported the EMS' opinion to consider also this set of metabolites as covered by the parent (i.e. at least as toxic as the parent). Therefore, reference values of the parent can apply to these metabolites, if required for consumer risk assessment.

3. Residues

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

3.1.1.1. Nature of residues

The metabolism of propargite in primary crops was investigated upon foliar or local applications on fruits (tomatoes, apples and peaches), root (potatoes) and cereals (maize) crop groups during the EU pesticides peer review and the MRL review (EFSA, 2011, 2013). The studies performed on peaches, potatoes and cereals were found to be unacceptable and are herewith reported for information only. The results from two new metabolism studies representative for the reported use on citrus and tea were assessed by the EMS (Italy, 2017). An overview of the available metabolism studies is presented in Table 1.

[11] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, pp. 1–1355.

Table 1: Summary of available metabolism studies in plants

Crop groups	Crops	Label position	Application	Sampling	Comments/source
Existing metabolism studies					
Fruit crops	Apple	^{14}C-phenyl-propargite	Direct onto fruit and leaf, 1 × 8.16 kg/ha	23 DAT	95:5 (*trans:cis*) mixture (EFSA, 2011)
	Tomato		Foliar, 1 × 0.86–1.71 kg/ha	15 DAT	
	Peach	^{14}C-phenyl-propargite	Direct onto fruit, 1 × 3.9 kg/ha	0, 10, 21 DAT	For information
Root crops	Potato		Foliar, 1 × 1.91 kg/ha	18 DAT	For information
Cereals/grass crops	Maize		Foliar, 1 × 2.80 or 11.20 kg/ha	21 (forage), 42 (ear, stover, husk, silk, cob, kernel) DAT	For information
Pulses/oilseeds	Bean with pod	^{14}C-phenyl-propargite	Foliar, 1 × 4.20 kg/ha	7 DAT	EFSA (2013)
New metabolism studies (OECD guidance 501)					
Fruit crops	Orange	^{14}C-cyclohexyl or ^{14}C-phenyl-propargite	Foliar, 1 × 69 or 208 mg/tree	7, 21 DAT	99:1 (*trans:cis*) mixture (Italy, 2017)
Miscellaneous	Tea	^{14}C-phenyl-propargite	Foliar, 2 × 0.61 or 1.84 kg/ha, interval 14 days	1, 3, 7 (lower rate only), 14 (both rates) DALA	

DAT: days after treatment; DALA: days after last application.

In the new metabolism studies on **oranges**, total radioactivity residue (TRR) was nearly all located in the peel (1.83–5.76 mg eq/kg) with little radioactivity in the pulp (0.003–0.016 mg eq/kg). Residues could be extracted with the 1–11% of TRR remaining in the post-extraction solid. Propargite was the major component of radiolabelled residues (42–93% TRR in peel and 33–67% TRR in pulp).

Metabolites identified were the hydroxylated product of propargite, TBPC, further hydroxylated (HOMe-TBPC) and carboxylated (carboxy-TBPC) present in various sugar conjugated forms. Only TBPC and HOMe-TBPC were found in the pulp (11–13% of TRR, 7 DAT). Apart from carboxy-TBPC-hexoside (20% TRR; 0.36 mg eq/kg, 21 DAT) and HOMe-TBPC-hexoside (12% TRR, 0.22 mg eq/kg, 21 DAT), none of the other identified metabolite was present in the peel at levels that individually exceeded 10% TRR.

Results of the new studies on oranges were consistent with previous metabolism studies on apple and tomato fruits (EFSA, 2013). Parent propargite represented the major component of the TRR (52–74% in tomatoes; 89% and 31% in apple peel and pulp, respectively). The intermediate product TBPC (2–14% TRR in tomatoes and apples) formed TBPC-diol and HOMe-TBPC-diol, which were observed in apple fruits (28% and 14% TRR, respectively) and carboxy-TBPC triol, which was found in tomatoes (31% TRR).

In the metabolism study on **tea**, total radioactivity in the leaves decreased over the 14-day time from 90 to 34 mg eq/kg (study at the GAP rate). Residues could be extracted with less than 10% TRR remaining as post-extract solid. Parent compound was the main component of residues (22–79% TRR) at each sampling time. It underwent extensive metabolism to form TBPC and HOMe-TBPC conjugated with various sugars. Each identified metabolite was present at levels that individually did not exceed 10% TRR, except HOMe-TBPC-glucoside (12% TRR, 4 mg eq/kg, 14 DALA). Carboxy-TBPC and carboxy-TBPC-triol were not observed in tea leaves.

In summary, in fruits and tea leaves parent propargite was identified in significant quantities. In oranges, considerable amounts were found on the peel with only low amounts of residues in the pulp. A number of metabolites conjugated with various sugars was formed with qualitative differences between tested crops, as carboxy-TBPC-triol was identified only in the tomato metabolism and carboxy-TBPC and carboxy-TBPC -triol were not observed in tea leaves. Although individually not exceeding 10%, the absolute amounts of the free and conjugated forms of the identified metabolites showed to be substantial. The metabolic profile following foliar application of propargite radiolabelled in either the phenyl or the cyclohexyl ring demonstrated that no cleavage occurred.

For enforcement, the residue definition as propargite for fruit crops and tea is appropriate. The residue definition currently set in Regulation (EC) No 396/2005 is identical.

For risk assessment, the EMS proposed the residue definition derived under Directive 91/414/EEC for fruit crops:

- Fruit crops: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC diol, carboxy-TBPC, carboxy-TBPC-diol, carboxy-TBPC triol, expressed as propargite.

On the ground that carboxy-TBPC and carboxy-TBPC triol were not detected in the metabolism study, while HOMe-TBPC-glucoside was a major metabolite and its presence was confirmed in the supervised residue trials, the EMS proposed a different residue definition for risk assessment in tea:

- Tea: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, HOMe-TBPC-glucoside, carboxy-TBPC-diol, expressed as propargite.

Studies investigating the effect of the metabolism on the isomer ratio were not performed. However, separate analysis of the *trans*-isomers and the *cis*-isomers of propargite showed that no significant changes occurred in the isomeric ratio of retained samples from field residue trials and processing studies with oranges and tea compared to the formulated product used to perform the trials. Thus, for the propargite assessed in this import tolerance request, an isomeric shift is not expected in orange and tea residues.

For the uses on citrus and tea and the composition of the active substance under assessment (ratio 99:1), EFSA concluded that the metabolism of propargite is sufficiently addressed and the proposed residue definitions for enforcement and risk assessment are applicable.

3.1.1.2. Magnitude of residues

To support the import tolerance request, field residue trials on oranges and tea were submitted. Samples were analysed for propargite and for all metabolites included in the residue definition proposed for risk assessment, except for TBPC-diol in tea. The applicant proposed to estimate the levels of this metabolite from the metabolism study conducted at the reported GAP in tea.[12] A similar approach was suggested for tomatoes in the EU pesticides peer review (EFSA, 2011) and considered acceptable.

a) Citrus fruits *(BR GAP: 1 × 72 g/hL, PHI 7 days)*

Ten GAP-compliant residue trials on orange trees conducted in Brazil over two seasons were submitted. Trials were half designed as decline trials.

According to the EU guidance, residue data on orange only are not sufficient to allow the extrapolation to the whole group of citrus fruits (European Commission, 2017). EFSA agreed with the conclusion of the EMS to set the MRL of 4 mg/kg for imported oranges only.

b) Tea (*IN GAP: 2 × 612 g/ha, PHI 7 days*).

Eight GAP-compliant residue trials on tea plants conducted in India and China in 2014 were submitted. Residues were analysed on fresh leaves and, after drying, in green and black tea. Based on the residues observed in black tea from the eight trials submitted and using the OECD MRL calculator, the MRL of 50 mg/kg is derived.

It is noted that the great variability present in each set of data (black tea: 0.14–32.20 mg/kg; green tea: 0.14–14.30 mg/kg) led to a MRL proposal significantly greater than the highest residue in green and black tea, which was detected as outlier (Dixon's Q test). These values are largely different to the others, being several magnitudes higher. If disregarded from the calculation, a MRL of 10 mg/kg is derived from the seven residue levels in green tea.

The results of the residue trials, the related risk assessment input values (highest residue, median residue) and the MRL proposals are summarised in Table 3. In addition, conversion factors for risk assessment derived from the submitted trials are reported in Table 4.

According to the EMS, the results of the residue trials were sufficiently supported by validated analytical methods and storage stability data. The trial samples were stored for a maximum period of 4 months (oranges) and 8 months (tea).

Freezer storage stability with propargite, TBPC and HOMe-TBPC in high acid content matrices were assessed during the EU pesticides peer review (EFSA, 2011). Additional storage stability data with

[12] Conversion factor used to estimate levels of TBPC-diol in residue trials: TBPC-diol/propargite (3.2%/47.1% TRR) = 0.068.

propargite, TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-glucoside and carboxy-TBPC in orange peel and pulp and/or tea were provided in this import tolerance request (Italy, 2017). An overview of the available storage stability data is provided in Table 2.

Studies investigating the stability of metabolites HOMe-TBPC-diol, carboxy-TBPC-diol and carboxy-TBPC-triol in high acid content matrices were not available. Nevertheless, since these metabolites were not observed in the metabolism study on oranges, this is not expected to have an impact on the MRL derived for this commodity.

The stability of metabolites HOMe-TBPC-diol, carboxy-TBPC-diol and TBPC-diol was not investigated in tea. However, as HOMe-TBPC, HOMe-TBPC-glucoside and carboxy-TBPC showed to be stable in this commodity and assuming that comparable behaviour is expected for the diol under frozen conditions (i.e. no pH interference, no enzymatic degradation activity), no degradation of these metabolites is expected to have occurred during samples storage. Since not analysed for, storage stability of TBPC-diol in tea matrix is not relevant to support the submitted residue data.

Table 2: Summary of storage stability data in high acid content and tea matrices

Compound	High acid content matrices		Tea matrix	
Propargite	12 months	Orange (EFSA, 2011)	8.5 months	Black/green
	4 months	Grapes/grapefruits (EFSA, 2011)		
TBPC	4 months	Orange peel/pulp	8 months	Black
	36 months	Grapes (EFSA, 2011)		
TBPC-diol	4 months	Orange peel/pulp	Not analysed for in residue trials	
HOMe-TBPC	4 months	Orange peel/pulp	8 months	Black
	36 months	Grapes (EFSA, 2011)		
HOMe-TBPC-diol	n.r. (not found in metabolism with orange)		No information	
HOMe-TBPC-glucoside	n.r. (not in residue definition)		8 months	Black
Carboxy-TBPC	4 months	Orange peel/pulp	n.r. (not in residue definition)	
Carboxy-TBPC-diol	n.r. (not found in metabolism with orange)		No information	
Carboxy-TBPC-triol	n.r. (not found in metabolism with orange)		n.r. (not in residue definition)	

n.r.: not relevant.

Storage stability data of propargite are also available in additional crop categories that are not relevant to the crops under assessment (high water content matrix: 12 months in apples, 8 months in tomatoes and 5 months in peaches; high oil content matrix: 12 months in hops).

EFSA concluded that the data (Table 3) are sufficient to derive the following MRL proposals:

- 4 mg/kg oranges imported from Brazil. MRL set in Brazil is higher (5 mg/kg).
- 50 mg/kg tea imported from India. There is no unequivocal evidence, but the MRL reported to be set in India is significantly lower (10 mg/kg). An explanation for the large difference was not given by the applicant. However, EFSA noticed that disregarding the highest value (statistically detected as outlier), a MRL of 10 mg/kg is derived from the other seven trials.

Table 3: Overview of the available residues trials data

Crop (GAPs)	Region/ indoor[a]	Residue levels observed in the supervised residue trials[b] (mg/kg)	Recommendations/comments[c]	MRL proposal (mg/kg)	HR[d] (mg/kg)	STMR[e] (mg/kg)
Orange	BR	**Mo**: 0.42; 0.80; 1.10; 1.20; 1.20; 1.30; 1.40; 1.40; 1.90; 1.90 Pulp: 9 × < 0.01; 0.01 **RA**: 0.53; 0.89; 1.20; 1.29; 1.30; 1.39; 1.49; 1.49; 1.99; 2.00 Pulp: 9 × < 0.10; 0.10	Residue trials compliant with reported GAP MRL_{OECD}: 3.79 (unrounded) **Metabolites, whole fruit:** TBPC: 4 × < 0.01; 2 × 0.01; 3 × 0.02; 0.03 TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, carboxy-TBPC, carboxy-TBPC-diol, carboxy-TBPC triol: 10 × < 0.01 **Metabolites, pulp:** 10 × < 0.01 (all)	4	(1.90) 2.00	(1.25) 1.34
Tea, black fermented and dried	IN	**Mo**: 0.19; 0.20; 0.43; 0.99; *2.73*; *3.06*; *3.54*; *32.20*[f]	Combined data set (U-test, 5%) of residue trials conducted in India and China compliant with reported GAP MRL_{OECD}: 49.04 (unrounded) (all 8 values) MRL_{OECD}: 7.45 (unrounded) (disregarding HR value)	**50**	(32.20)	(1.86)
		RA: 1.85; 6.06; 8.55; 10.52; *17.95; 21.86; 32.43; 61.27*	**Metabolites:** TBPC: 0.19; 1.02; 1.20; 1.72; 1.75; 2.72; 4.68; 5.84 TBPC-diol (estimated): 2 × 0.01; 0.03; 0.07; 0.19; 0.21; 0.24; 2.19 HOMe-TBPC: 0.28; 0.49; 1.62; 1.78; 3.24; 4.64; 6.12; 7.44 HOMe-TBPC glucoside: 1.20; 4.24; 4.26; 4.48; 10.80; 2 × 11.90; 14.70 HOMe-TBPC-diol, carboxy-TBPC-diol: 8 × < 0.01		**61.27**	**14.24**
Tea, green dried		**Mo**: 0.14; 0.19; 0.39; 1.17; *3.14*; *3.33*; *4.98*; *14.30*[f]	Combined data set (U-test, 5%) of residue trials conducted in India and China compliant with reported GAP MRL_{OECD}: 22.36 (unrounded) (all 8 values) MRL_{OECD}: 9.55 (unrounded) (disregarding HR value)	30	(14.30)	(2.16)
		RA: 1.82; 2.35; 2.65; 5.15; *12.64;14.73*; *15.51; 28.57*	**Metabolites:** TBPC: 0.44; 0.76; 0.79; 1.12; 2 × 1.41; 1.46; 1.68 TBPC-diol (estimated): 2 × 0.01; 0.03; 0.08; 0.21; 0.23; 0.34; 0.97 HOMe-TBPC: 0.04; 0.06; 0.12; 0.13; 0.17; 2 × 0.18; 0.23 HOMe-TBPC glucoside: 1.15;1.16; 1.18; 2.55; 8.51; 8.59; 11.20; 13.00 HOMe-TBPC-diol, carboxy-TBPC-diol: 8 × < 0.01		28.57	8.90

GAP: Good Agricultural Practice; MRL: maximum residue level; OECD: Organisation for Economic Co-operation and Development.
(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): Individual residue levels of propargite considered for MRL calculation are reported in ascending order. Residue levels of metabolites are expressed as individual component equivalents and in ascendant order.
Mo: residue level according to the residue definition for monitoring (propargite);
RA: residue level according to the residue definition for risk assessment.
The following conversion factors (molecular weight propargite/molecular weight metabolite) were used to express residues of each metabolite as propargite equivalents:
TBPC: 1.41 TBPC-diol: 1.33 HOMe-TBPC: 1.33 HOMe-TBPC diol: 1.25 HOMe-TBPC glucoside: 0.82
carboxy-TBPC: 1.26 carboxy-TBPC-diol: 1.19 carboxy-TBPC-triol: 1.13
(c): Any information/comment supporting the decision. Underlined values: higher residue from samples taken at a PHI longer than the reported PHI. In italics, residues from trials on tea conducted in China. Residues of TBPC-diol in tea were estimated using a CF of 0.068 based on the metabolism study at the reported GAP.
(d): HR: Highest residue level according to the residue definition for risk assessment. Values into parentheses indicate the HR according to residue definition for monitoring.
(e): STMR: Median residue level according to residue definition for risk assessment. Values into parentheses indicate the STMR according to residue definition for monitoring.
(f): Values on black and green tea measured in one Chinese trial statistically detected as outliers (Dixon's Q test). MRL_{OECD} proposal without these values: 8 mg/kg (black tea), 10 mg/kg (green tea).

EFSA derived conversion factors (CF) for risk assessments at the different preharvest intervals (PHI) by summing up each component (as propargite equivalent) included in the residue definitions proposed for risk assessment (including values at LOQ).[13] This approach will most probably lead to overestimated results for oranges. The reported CFs for tea should be considered as indicative, due to the limitation in the storage stability data for the diol-conjugate components and the estimation of TBPC-diol residues in field trials based on the metabolism study. The CF values are summarised in Table 4.

Table 4: Median CF for risk assessment calculated at the different pre-harvest intervals

PHI[(a)] (days)	0	3	7	10	14	Comments
Orange (whole fruit)	1.07	1.06	1.07	1.06	1.09	Calculated from 4 samples at all PHIs, except at PHI 7 days (10 samples)
Tea, black	1.28	2.04	9.45	7.92	19.57	Calculated from 2 samples at all PHIs, except at PHI 7 and 14 days (8 samples)
Tea, green	1.15	1.82	4.53	4.02	14.07	Calculated from 2 samples at all PHIs, except at PHI 7 and 14 days (8 samples)

Conversion factors (CF) calculated at the supported PHI are underlined.
(a): Plant harvest interval (PHI): 0 for samples collected just after the last application.

Based on these data, the following overall CFs are proposed for risk assessment:

- Oranges: 1.07
- Tea: 15 (indicative)

3.1.1.3. Effect of industrial processing and/or household preparation

The effect of processing on the nature of propargite residues was assessed by the EMS in the framework of this import tolerance request (Italy, 2017). The standard hydrolysis study submitted deviated from the OECD guidance 507 as investigated only ^{14}C-phenyl-propargite. The results are summarised in Table 5.

Table 5: Results of the hydrolysis study

Conditions	Propargite (% AR)	TBPC (% AR)
Pasteurisation (20 min, 90°C, pH 4)	96.2	3.8
Baking, brewing and boiling (60 min, 100°C, pH 5)	93.7	6.3
Sterilisation (20 min, 120°C, pH 6)	27.8	72.2

AR: applied radioactivity.

Propargite showed to be hydrolytically stable under the conditions representative for pasteurisation and baking/brewing/boiling, whereas degraded to the metabolite TBPC under conditions simulating sterilisation, still representing about the 30% of the applied radioactivity. Hydrolysis studies covering all the compounds included in the residue definition for risk assessment are in principle required. However, considering that the stability of TBPC is covered by the available hydrolysis study and that all other metabolites are structurally similar to TBPC, it can be assumed that, following standard hydrolysis conditions, metabolites considered for risk assessment will have a similar behaviour. Therefore no other relevant compound is expected to be formed during processing.

Residues before and after processing were analysed for all the components included in the residue definition for risk assessment proposed for primary crops (except TBPC-diol in tea) with comparable levels. For the processed orange and tea products assessed, the same residue definitions as proposed for raw agricultural commodities (RAC) are applicable.

Specific processing studies with oranges and tea were provided (Italy, 2017). The distribution of residues into orange peel and pulp was investigated in the samples from residue trials and from processing studies. Peeling factors ranged from 0.01 to 0.08 (median of 0.01).

For **oranges**, the results from three overdosed (5N) studies processing oranges into juice and pomace and two studies (1N and 3N in side-by-side plots) into juice were submitted. In the processing studies at 5N the GAP, residues of propargite and TBPC were observed in both the raw and processed

[13] The EMS counted as zero HOMe-TBPC-diol and carboxy-TBPC-diol, which were not measured in the residue trials, in the CF calculation (Italy, 2017).

commodities, with concentration in pomace but not in fresh juice produced from peeled fruits. Except HOMe-TBPC, which residues were at levels close to the LOQ in two dry pomace samples, the other metabolites included in the residue definition for risk assessment of fruit crops were not quantifiable in both raw fruit and processed products. The other two processing studies at 1N and 3N the GAP were analysed only for propargite, which showed not to concentrate in juice.

For **tea**, the results from four studies conducted at 2N the GAP rate with samples collected at a longer PHI of 14 days and dried black and green leaves processed into infused and instant tea were submitted. Samples were not analysed for the metabolite TBPC-diol. HOMe-TBPC-diol was not found (< 0.01 mg/kg) in dried tea and both processed products. In black and green brewed tea, residues of propargite and the metabolites included in the residue definition for risk assessment of tea crop were not found, except HOMe-TBPC in one sample. In black and green instant tea, residues of HOMe-TBPC, HOMe-TBPC-glucoside showed to concentrate, whereas carboxy-TBPC-diol was quantified (up to 0.08 mg/kg) in the processed product only.

Samples from the processing studies were stored for the period covered by available storage stability data except in case of instant tea, where samples were stored up to 13 months. The reliability of the derived median PF for instant tea should therefore be reconsidered when supported by stability data covering the whole length of the storage of the samples.

Robust processing factors (PF) were derived from the studies on oranges and brewed tea.

Robust CF from enforcement to risk assessment[14] could only be calculated for orange juice and dry pomace. In particular for instant tea, as residues of propargite were below or close to the LOQ in the processed commodity, it was not possible to calculate reliable CF from enforcement to risk assessment. Moreover, these samples were collected at a longer PHI, not analysed for TBPC-diol and not supported by storage stability data. If CFs were to be required by risk managers, in particular for risk assessment purposes, additional information would be needed. The processing factors and conversion factors derived are summarised in Table 6.

Table 6: Overview of the available processing studies

Crop (RAC)/edible part or Crop (RAC)/ processed product	Number of studies	Processing factor (PF)		Conversion factor (CF) for RA[(a)]
		Individual values	Median PF	
Orange, peeling	13	9 × 0.01; 0.02; 0.03; 0.04; 0.08	0.01	–
Orange, fresh juice (peeled)	3	0.02; 0.05; 0.08	0.05	2.11
	2	0.02; 0.05	0.04	–
Orange, dry pomace	3	3.94; 4.95; 6.42	4.95	1.21
Tea, brewed	4	< 0.02 (black)[(b)]; < 0.02; < 0.59 (green)	0.02	–
Tea, instant	4	< 0.02 (black)[(b)]; 0.04; < 0.59 (green)	0.04[(c)] (indicative)	–

(a): When the residue definition for risk assessment differs from the residue definition for monitoring.
(b): A study on black tea with no quantifiable residues of propargite in the raw commodity was disregarded.
(c): Indicative as potential residues of TBPC-diol in RAC and processed products not considered in the calculation.

The median PFs derived for tea are in line with the mean PF of 0.02 for brewed black tea and 0.03 for instant tea derived at PHI 7 days by JMPR (FAO, 2002).

EFSA recommended the inclusion of the derived PFs of 0.05 for orange juice and 0.02 for brewed tea in Annex VI of Regulation (EC) No 396/2005.

3.1.2. Rotational crops

The residues of propargite and its metabolites in rotational crops are not of relevance for the assessment of import tolerances.

3.2. Nature and magnitude of residues in livestock

Orange dry pulp may be used for feed purpose. Since the processing of imported oranges cannot be excluded, the possible transfer of residues in products of animal origin shall be investigated.

[14] Calculated as residue level in processed fraction (expressed according to RD-RA)/Residue level in processed fraction (expressed according to RD-Mo).

3.2.1. Dietary burden of livestock

EFSA calculated the livestock dietary burden for cattle and pigs only. According to the feeding tables listed in the OECD guidance (OECD, 2013), dry pulp is not usually fed to sheep and poultry. This by-product is also not listed as feed item for fishes (European Commission, 2013). At EU level, propargite is currently not approved for use in plant protection products. Therefore orange dry pulp is the only feed item to be considered in the calculation. The STMR derived for oranges according to the residue definition for enforcement as multiplied by the PF and the CF for enforcement to risk assessment derived for dry pomace was used to estimate the potential transfer of residues. The input value for the dietary burden calculation are summarised in Table 7 and the estimated animal dietary intakes in Table 8.

Table 7: Input values for the dietary burden calculation

Feed commodity	Median dietary burden		Maximum dietary burden	
	Input (mg/kg)	Comment	Input (mg/kg)	Comment
Orange, dry pulp	7.49 (1.25 × 4.95 × 1.21)	STMR × PF × CF	7.49 (1.25 × 4.95 × 1.21)	STMR × PF × CF

STMR: supervised trials median residue; PF: processing factor; CF: conversion factor.

Table 8: Results of the dietary burden calculation

Relevant groups	Dietary burden expressed in				Most critical diet[(a)]	Most critical commodity		Trigger exceeded (Yes/no)
	mg/kg bw/day		mg/kg DM					0.004
	Median	Maximum	Median	Maximum				mg/kg bw
Cattle (beef)	0.010	0.010	0.41	0.41	Dairy cattle	Citrus	Dried pulp	Yes
Cattle (dairy)	0.063	0.063	1.65	1.65	Dairy cattle	Citrus	Dried pulp	Yes
Swine (breeding)	0.028	0.028	1.23	1.23	Breeding swine	Citrus	Dried pulp	Yes

bw: body weight; DM: dry matter.
(a): Considering the maximum dietary animal burden.

The calculated dietary burdens exceeded the trigger value of 0.004 mg/kg bw per day for both cattle and swine, therefore the nature of residues was investigated.

3.2.2. Nature of residues

The applicant conducted a new metabolism study in lactating goats, supplemented by the metabolism studies assessed in the framework of the MRL review (EFSA, 2013). An overview of the available metabolism studies is presented in Table 9.

Table 9: Summary of available metabolism studies in ruminants

Species	Label position	No of animal	Application rate and duration	Sampling details		Comments
				Sample	Time	
Existing metabolism study						
Lactating goat	^{14}C-phenyl-propargite	2	3.3 mg/kg bw × 3 days 13.6 mg/kg bw × 3 days	Milk	2 × day	EFSA (2013)
				Urine, faeces	1 × day	
				Tissues	8 h after sacrifice	

Species	Label position	No of animal	Application rate and duration	Sampling details		Comments
				Sample	Time	
New metabolism study (OECD guidance 503)						
Lactating goat	^{14}C-cyclohexyl propargite	1	39.0 mg/kg DM × 5 days	Milk	2 × day	Rate equal to 24N (cattle) and 32N (pig) the calculated maximum burden
				Urine, faeces	1 × day	
				Tissues	22 h after sacrifice	

bw: body weight; DM: dry matter.

In the new metabolism study conducted with the compound radiolabelled in the cyclohexyl ring, the majority of the applied radioactivity (AR) was recovered in the urine, faeces and gastrointestinal tract (96% AR) with low amount in milk (0.5% AR). Highest radioactive residues were found in liver (0.3% AR) followed by the kidney (0.2% AR), fat (0.04% AR) and muscle (0.01% AR). Milk residues reached the highest level at Day 4 of the study (0.09 mg eq/kg in skimmed milk and 0.60 mg eq/kg in milk fat).

Propargite was predominant in fatty milk (up to 69% TRR) and present in muscle and fat (11–29% TRR). The major metabolites were HOMe-TBPC-diol (40% TRR) in muscle, TBPC-diol and free and conjugated HOMe/carboxy-TBPC (30%) in fat. In liver and kidney, amounts of propargite were low, indicating a more extensive metabolism in these organs. Predominant residues were free and glucuronide HOMe-TBPC-diol and carboxy-TBPC (11–17% TRR). The metabolic pathway is in line with the results from the metabolism study conducted with phenyl-radiolabelled propargite (EFSA, 2013) and with the metabolic pathway observed in laboratory animals. Therefore a metabolism study in pigs is not required.

Based on the results of the metabolism studies, propargite is most likely not a good marker for enforcement in liver and kidney. However, considering that at the calculated dietary burden, residues in cattles and swine tissues and in milk are expected to remain below the LOQ (see Section 3.2.3), EFSA agrees with the EMS that the current residue definition in Regulation (EC) No 396/2005 as propargite can be still considered valid in the present assessment.

EFSA concluded that the metabolism of propargite in ruminants was sufficiently elucidated. The submitted study confirmed that the residues are mainly accumulating in fat and therefore, propargite shall be classified as fat-soluble.

3.2.3. Magnitude of residues

Based on the results of the metabolism studies conducted at 24N (cattle) and 32N (pig), the maximum burdens for cattle and pigs, at the calculated dietary burdens significant residues (> 0.01 mg/kg) of propargite in livestock commodities are not expected. Therefore, the setting of MRLs in products of animal origin is not required based on the reported use on oranges in Brazil.

The feeding study in cows assessed in the DAR (France, 2007) but not peer reviewed is confirming that residues of the active substance propargite are not expected in livestock products. At the lower dose rate tested of 50 mg/kg dry matter (DM) per day, representing 30N (cattle) and 41N (pigs) the calculated maximum burdens, residues of propargite ranged from < 0.01 to 0.20 mg/kg. Residues of TBPC and Home-TBPC, the only compounds analysed for, were below or close to the LOQ, except in liver (0.19 mg/kg).

4. Consumer risk assessment

The consumer risk assessment was performed with revision 2 of the EFSA PRIMo. This exposure assessment model contains the relevant European food consumption data for different sub-groups of the EU population[15] (EFSA, 2007).

To calculate the chronic exposure, EFSA used median residue (STMR) values derived from the residue trials conducted on the two crops under consideration in this import tolerance request and reported in Table and the peeling factor for oranges. The remaining commodities of plant and animal

[15] The calculation of the long-term exposure (chronic exposure) is based on the mean consumption data representative for 22 national diets collected from MS surveys plus 1 regional and 4 cluster diets from the WHO GEMS Food database; for the acute exposure assessment the most critical large portion consumption data from 19 national diets collected from Member States surveys are used. The complete list of diets incorporated in EFSA PRIMo is given in its reference section (EFSA, 2007).

origin were excluded from the exposure calculation. Residues from other sources are not expected since no use of propargite on plants is currently authorised in the EU.

The acute exposure assessment was performed only with regard to oranges and tea assuming the consumption of a large portion of the food items as reported in the national food surveys and that these items contained residues at the HR (orange) or the STMR (tea) level as observed in supervised field trials (Table 4) and corrected for the peeling factor for oranges. A variability factor of 7 accounting for the inhomogeneous distribution on the individual items consumed was included in the calculation for oranges (EFSA, 2007).

The input values used for the dietary exposure calculation are summarised in Table 10.

Table 10: Input values for the consumer dietary exposure assessment

Commodity		Chronic exposure assessment		Acute exposure assessment	
		Input (mg/kg)	**Comment**	**Input (mg/kg)**	**Comment**
Risk assessment residue definition: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC diol, carboxy-TBPC, carboxy-TBPC-diol, carboxy-TBPC triol, expressed as propargite (all isomers)					
Oranges		0.013 (1.34 × 0.01)	STMR-RA × Peeling F	0.02 (2 × 0.01)	HR-RA × Peeling F
Risk assessment residue definition: sum of propargite and metabolites TBPC, TBPC-diol, HOMe-TBPC, HOMe-TBPC-diol, HOMe-TBPC-glucoside, carboxy-TBPC-diol, expressed as propargite (all isomers)					
Tea	MRL 50 mg/kg	14.24	STMR-RA	61.27	HR-RA (8 trials)
	MRL 10 mg/kg			32.43	HR-RA (7 trials)

STMR: supervised trials median residue; RA: risk assessment; HR: highest residue; MRL: maximum residue level.

The estimated exposure was then compared with the toxicological reference values derived for propargite (see Section 2). The results of the intake calculation using the EFSA PRIMo is a key supporting document and is made publicly available as a background document to this reasoned opinion.

A long-term consumer intake concern was not identified for any of the European diets incorporated in the EFSA PRIMo. The total calculated chronic intake accounted for 6.3% of the ADI (IE, adult). The contribution of residues in oranges and tea to the total consumer exposure was less than 0.2% (oranges) and 6.2% (tea) of the ADI. An acute consumer risk was not identified as well. The highest acute consumer exposure was calculated to be 4% of the ARfD for oranges. For tea, acute consumer risk was estimated as 94% of the ARfD considering the whole set of eight trials supporting a MRL proposal of 50 mg/kg and 50% of the ARfD when the MRL proposal is of 10 mg/kg based on seven trials. The diet was the UK infant in all cases.

EFSA concluded that the use of propargite on oranges and tea as authorised in the exporting countries will not result in a consumer exposure exceeding the toxicological reference values and therefore is unlikely to pose a consumer health risk.

EFSA also acknowledged that there are uncertainties in the risk assessment regarding:

- EFSA emphasised that there is no final FAO specification nor agreed EU specification for propargite and the name propargite may apply to several of the possible stereo-isomers of the compound. EFSA considered the genotoxic potential of propargite technical material as a whole (i.e. active substance and associated impurities) since genotoxicity studies on individual impurities are not available. Therefore, the present assessment is expected to cover technical propargite as used in the studies considered in this import request and containing a trans:cis isomer ratio of 99:1.
- The toxicological profile of some of the metabolites included in the residue definition. As there are no indications that they should be of higher toxicity than the parent, overall EFSA supported the EMS' opinion to consider also this set of metabolites as covered by the parent.
- The stability of the metabolites included in the residue definition for risk assessment following processing. Although the stability of TBPC is expected to be addressed by the available hydrolysis study, a standard hydrolysis study performed with all other metabolites included in the residue definition for risk assessment was not available.
- The full reliability of the residue levels of some of the metabolites included in the residue definition for tea. Although the components containing the HOMe-TBPC and carboxy-TBPC structure showed to be stable, the stability of their respective diol conjugates in tea matrix was not addressed. Moreover TBPC-diol was not analysed for in the residue trials and levels estimated based on the metabolism study.

Conclusions and recommendations

The information submitted was sufficient to propose the MRLs summarised in the table below:

Code[(a)]	Commodity	Existing EU MRL (mg/kg)	Proposed EU MRL (mg/kg)	Comment/justification
Enforcement residue definition: Propargite[(F)]				
0110020	Oranges	0.01*	4	Import tolerance supported by data. The MRL set in Brazil is 5 mg/kg Unlikely to pose a consumer health risk
0610000	Tea	0.05*	Risk manager option	Import tolerance supported by data Based on the residue trials an MRL of 50 mg/kg for tea could be derived. However, a risk manager decision is required whether the setting of a MRL of 50 mg/kg for tea is acceptable since the MRL reported to be into force in India is 10 mg/kg. It is noticed that disregarding the highest value (statistically detected as outlier) a MRL of 10 mg/kg is derived from the remaining seven trials on tea Unlikely to pose a consumer health risk

MRL: maximum residue level.
*: 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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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
CAC	Codex Alimentarius Commission
CAS	Chemical Abstract Service
CF	conversion factor for enforcement to risk assessment residue definition
CV	coefficient of variation (relative standard deviation)
CXL	Codex maximum residue limit
DALA	days after last application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
EC	emulsifiable concentrate
EMS	evaluating Member State
eq	residue expressed as a.s. equivalent
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
GC	gas chromatography
GC–MS	gas chromatography with mass spectrometry
HPLC–MS/MS	high-performance liquid chromatography with tandem mass spectrometry
HR	highest residue
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
LOQ	limit of quantification
MRL	maximum residue level
NEU	northern Europe
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PF	processing factor
PHI	preharvest interval
PRIMo	(EFSA) Pesticide Residues Intake Model
QSAR	quantitative structure–activity relationship
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
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
STMR	supervised trials median residue

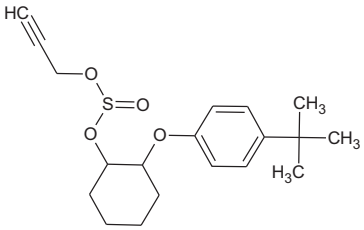
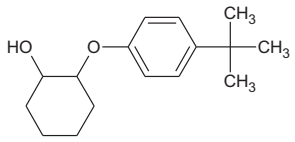
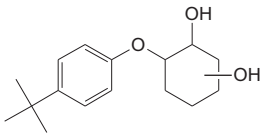
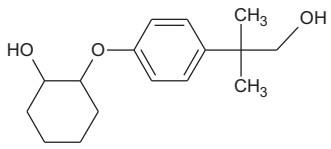
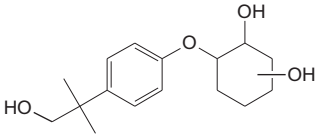
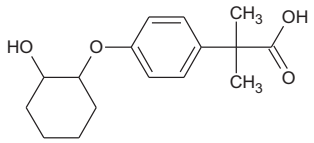
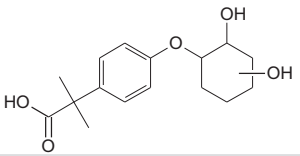
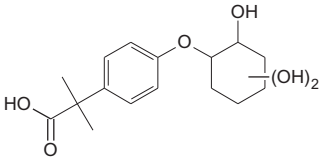
TAR	total applied radioactivity
TGR	transgenic rodent assay
TRR	total radioactive residue
WHO	World Health Organization

Appendix A – Good Agricultural Practice (GAPs)

Crop and/or situation	NEU, SEU, MS or country	F G or I[a]	Pests or group of pests controlled	Preparation		Application				Application rate per treatment			PHI (days)[d]	Remarks
				Type[b]	Conc. a.s.	Method kind	Range of growth stages and season[c]	Number min–max	Interval between application (min)	g a.s./hL min–max	Water L/ha min-max	g a.s./ha min–max		
Citrus	BR	F	*Phyllocoptruta oleivora* *Brevipalpus phoenicis* *Panonychus citri* *Eutetranychus banksi*	EC	720 g/L	Foliar spray	Not defined	1	–	72	–	–	7	
Tea	IN	F	Red spider mite, pink mite, purple mites, scarlet mites	EC	570 g/L	Foliar spray	Not defined	2	14 days	108–153	400	430–612	7	

NEU: northern European Union; SEU: southern European Union; MS; Member State or Country code: if non-EU trials; a.s.: active substance; EC: emulsifiable concentrate.
(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.
(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 – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
Propargite	(1*RS*,2*RS*;1*RS*,2*SR*)-2-(4-*tert*-butylphenoxy) cyclohexyl prop-2-ynyl sulfite CC(C)(C)c1ccc(cc1)OC2CCCCC2OS(=O)OCC#C ZYHMJXZULPZUED-UHFFFAOYSA-N	
TBPC	(1*RS*,2*RS*;1*RS*,2*SR*)-2-(4-*tert*-butylphenoxy) cyclohexan-1-ol CC(C)(C)c1ccc(cc1)OC2CCCCC2O FTIXUILRMBSXNS-UHFFFAOYSA-N	
TBPC-diol	4-[4-(2-methyl-2-propanyl)phenoxy]-1,x-cyclohexanediol or 4-(4-*tert*-butylphenoxy)-1,x-cyclohexanediol Unstated stereochemistry	
HOMe-TBPC	(1*RS*,2*RS*;1*RS*,2*SR*)-2-[4-(1-hydroxy-2-methylpropan-2-yl)phenoxy]cyclohexan-1-ol CC(C)(CO)c1ccc(cc1)OC2CCCCC2O KSXYDDBEXBLRMB-UHFFFAOYSA-N	
HOMe-TBPC diol	4-[4-(1-hydroxy-2-methyl-2-propanyl)phenoxy]-1,**x**-cyclohexanediol Unstated stereochemistry	
Carboxy-TBPC	2-(4-{[(1*RS*,2*RS*;1*RS*,2*SR*)-2-hydroxycyclohexyl]oxy} phenyl)-2-methylpropanoic acid O=C(O)C(C)(C)c1ccc(cc1)OC2CCCCC2O PNFIBUIZMXFFBQ-UHFFFAOYSA-N	
Carboxy-TBPC-diol	2-{4-[(2,**x**-dihydroxycyclohexyl)oxy]phenyl}-2-methylpropanoic acid Unstated stereochemistry	
Carboxy-TBPC triol	2-methyl-2-{4-[(2,**x,y**-trihydroxycyclohexyl)oxy] phenyl}propanoic acid Unstated stereochemistry	

SMILES: simplified molecular-input line-entry system.