EFSA Journal

CONCLUSION ON PESTICIDES PEER REVIEW

APPROVED: 16 June 2020

doi: 10.2903/j.efsa.2020.6189

Updated peer review of the pesticide risk assessment for the active substance dithianon in light of confirmatory data submitted

European Food Safety Authority (EFSA),
Maria Anastassiadou, Maria Arena, Domenica Auteri, Alba Brancato, Laszlo Bura, Luis Carrasco Cabrera, Eugenia Chaideftou, Arianna Chiusolo, Federica Crivellente, Chloe De Lentdecker, Mark Egsmose, Gabriella Fait, Luna Greco, Alessio Ippolito, Frederique Istace, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Alfonso Lostia, Christopher Lythgo, Oriol Magrans, Iris Mangas, Ileana Miron, Tunde Molnar, Laura Padovani, Juan Manuel Parra Morte, Ragnor Pedersen, Hermine Reich, Miguel Santos, Rachel Sharp, Alois Stanek, Juergen Sturma, Csaba Szentes, Andrea Terron, Manuela Tiramani, Benedicte Vagenende and Laura Villamar-Bouza

Abstract

The conclusions of the EFSA following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State, Greece, for the pesticide active substance dithianon are reported. The context of the peer review was that requested by the European Commission following the submission and evaluation of confirmatory mammalian toxicology and residues data. The conclusions were reached on the basis of the evaluation of the representative uses of dithianon as a fungicide on table and wine grapes and on pome fruit. The reliable endpoints concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and literature in the dossier peer reviewed, are presented. Concerns are identified.

Keywords: dithianon, peer review, confirmatory data, risk assessment, pesticide, fungicide

Requestor: European Commission

Question number: EFSA-Q-2020-00010

Correspondence: pesticides.peerreview@efsa.europa.eu

Update: This scientific output, approved on 16 June 2020, supersedes the previous output published on 12 November 2015 (EFSA, 2015).

Suggested citation: EFSA (European Food Safety Authority), Anastassiadou M, Arena M, Auteri D, Brancato A, Bura L, Carrasco Cabrera L, Chaideftou E, Chiusolo A, Crivellente F, De Lentdecker C, Egsmose M, Fait G, Greco L, Ippolito A, Istace F, Jarrah S, Kardassi D, Leuschner R, Lostia A, Lythgo C, Magrans O, Mangas I, Miron I, Molnar T, Padovani L, Parra Morte JM, Pedersen R, Reich H, Santos M, Sharp R, Stanek A, Sturma J, Szentes C, Terron A, Tiramani M, Vagenende B and Villamar-Bouza L, 2020. Updated peer review of the pesticide risk assessment for the active substance dithianon in light of confirmatory data submitted. EFSA Journal 2020;18(9):6189, 19 pp. https://doi.org/10.2903/j.efsa.2020.6189

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

Dithianon was included in Annex I to Directive 91/414/EEC on 1 June 2011 by Commission Directive 2011/41/EU, and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on the storage stability and the nature of residues in processed products, the aquatic and groundwater exposure assessment for phthalic acid and the risk assessment for aquatic organisms with respect to phthalic acid, phthalaldehyde and 1,2 benzenedimethanol by 31 May 2013.

In accordance with the specific provision, the applicant, BASF SE, submitted an updated dossier in May 2013, which was evaluated by the designated rapporteur Member State (RMS), Greece, in the form of an addendum to the draft assessment report. In compliance with guidance document SANCO 5634/2009 rev.4.5, the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 5 December 2013. The RMS collated all comments in the format of a reporting table, which was submitted to the European Commission in July 2014.

Following consideration of the comments received, the European Commission requested EFSA to organise a peer review of the RMS's evaluation of the confirmatory data submitted in relation to the nature of residues in processed products and the toxicological assessment of the processing metabolites and to deliver its conclusions.

EFSA published its conclusion on the peer review of the pesticide risk assessment in light of confirmatory data submitted in November 2015. A data gap was identified to address the magnitude of residues of metabolites Reg. No. 4005234 (phthalic acid), Reg. No. 4107273, Reg. No. 31062 and Reg. No. 4110933 in processed commodities. Pending the outcome of this data gap, toxicological data would be needed to address the genotoxicity profile of metabolites Reg. No 4005234 and Reg. No 4107273 and the toxicity profile of the identified metabolites recovered at significant levels in processing studies.

Given the data gaps identified for storage stability data on dithianon residues in grape wine, and for the magnitude of the metabolites Reg. No. 4107273, Reg. No. 31062, Reg. No. 4005234 (phthalic acid) and Reg. No. 4110933 in apple and grapes processed commodities, the consumer exposure assessment could not be concluded on and was identified as a critical area of concern. An acute intake concern has already been identified for table grapes (149% acute reference dose (ARfD)) in the previous EFSA conclusion.

In the meantime, the applicant conducted additional studies, in which the RMS has evaluated in a second addendum to the DAR in September 2018 and later in July 2019, revised in February 2020. The Commission requested EFSA to review the additional assessment made by the RMS based on the submitted data by the applicant and to deliver its conclusion by 15 June 2020.

Confirmatory data submitted in relation with the mammalian toxicology were discussed at the Pesticides Peer Review Meeting 25 in March 2020. In particular, the grouping, genotoxicity potential and the general toxicity of metabolites 1,4-naphthoquinone (Reg No. 4107273), phthalic acid (Reg No.4005234), Reg No. 4110904, Reg No. 31062 and Reg No. 4110933 were discussed. It was concluded that metabolites 1,4-naphthoquinone (Reg No. 4107273), phthalic acid (Reg No.4005234), Reg No. 4110904, Reg No. 31062 and Reg No. 4110933 are unlikely to be genotoxic. As the use of the threshold of toxicological concern (TTC) approach cannot be applied in this context, a complete consumer risk assessment cannot be finalised, and a data gap is set regarding the general toxicity potential of metabolites 1,4-naphthoquinone (Reg No. 4107273) and phthalic acid (Reg No.4005234).

In the residue section, data gaps were identified in the framework of the assessment of the confirmatory data. The data gap for storage stability data on dithianon residues in grape wine was not addressed whilst sufficient and acceptable processing trials to determine the magnitude of residues of the metabolites Reg. No. 4107273, Reg. No. 31062, Reg. No. 4005234 (Phthalic acid) and Reg. No. 4110933 in apple and grapes processed commodities have been provided. Given the identified data gap to address the general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) recovered at significant levels in apples and grapes processed commodities, the residue definition for monitoring and risk assessment in processed commodities remain open and the consumer dietary risk assessment cannot be finalised. An acute intake concern has already been identified for table grapes (149% ARfD) in the previous EFSA conclusions according to PRIMo rev.2A (EFSA, 2010, 2015). According to EFSA_PRIMo_rev.3.1 Model, a chronic intake concern was identified for the representative uses on pome fruit and table and wine grapes (IEDI: 109% acceptable daily intake (ADI) (NL toddler)) whilst an acute intake concern was confirmed for table grapes (IESTI: 165% ARfD) and further identified for pears (IESTI: 118% ARfD).

Table of contents

Background

Dithianon was included in Annex I to Directive 91/414/EEC[1] on 1 June 2011 by Commission Directive 2011/41/EU[2], and has been deemed to be approved under Regulation (EC) No 1107/2009[3], in accordance with Commission Implementing Regulation (EU) No 540/2011[4], as amended by Commission Implementing Regulation (EU) No 541/2011[5]. EFSA previously finalised a Conclusion on this active substance on 15 November 2010 (EFSA, 2010).

It was a specific provision of the approval that the applicant was required to submit to the European Commission further studies on the storage stability and the nature of residues in processed products, the aquatic and groundwater exposure assessment for phthalic acid and the risk assessment for aquatic organisms with respect to phthalic acid, phthalaldehyde and 1,2 benzenedimethanol by 31 May 2013.

In accordance with the specific provision, the applicant, BASF SE, submitted an updated dossier in May 2013, which was evaluated by the designated rapporteur Member State (RMS), Greece, in the form of an addendum to the draft assessment report. In compliance with guidance document SANCO 5634/2009 rev.4.5 (European Commission, 2011), the RMS distributed the addendum to Member States, the applicant and EFSA for comments on 5 December 2013. The RMS collated all comments in the format of a reporting table, which was submitted to the European Commission in July 2014.

Following consideration of the comments received, the European Commission requested EFSA to organise a peer review of the RMS's evaluation of the confirmatory data submitted in relation to the nature of residues in processed products and the toxicological assessment of the processing metabolites.

Following the commenting on the assessment of confirmatory data, the applicant provided substantial comments in the column 3 of the reporting table and the RMS prepared an updated addendum (Greece, 2014). In order to give Member States the opportunity to comment on this new information and assessment, a consultation took place with Member States via a written procedure in June–July 2015.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in September–October 2015.

EFSA published its conclusion on the peer review of the pesticide risk assessment in light of confirmatory data submitted in November 2015 (EFSA, 2015). A data gap was identified to address the magnitude of residues of metabolites Reg. No. 4005234 (phthalic acid), Reg. No. 4107273, Reg. No. 31062 and Reg. No. 4110933 in processed commodities. Pending the outcome of this data gap, toxicological data would be needed to address the genotoxicity profile of metabolites Reg. No 4005234 and Reg. No 4107273 and the toxicity profile of the identified metabolites recovered at significant levels in processing studies.

Given the data gaps identified for storage stability data on dithianon residues in grape wine, and for the magnitude of the metabolites Reg. No. 4107273, Reg. No. 31062, Reg. No. 4005234 (phthalic acid) and Reg. No. 4110933 in apple and grapes processed commodities, the consumer exposure assessment could not be concluded on and this was identified as a critical area of concern. An acute intake concern has already been identified for table grapes (149% ARfD) in the previous EFSA conclusion.

In the meantime, the applicant conducted additional studies, in which the RMS has evaluated in a second addendum to the draft assessment report in September 2018 and later in August 2019. The Commission requested EFSA to review the additional assessment made by the RMS based on the submitted data by the applicant and to deliver its conclusion by 31 May 2020. EFSA distributed the addendum to the draft assessment report to the Member States for consultation and comments on

[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 2011/41/EU of 11 April 2011 amending Council Directive 91/414/EEC to include dithianon as active substance and amending Commission Decision 2008/934/EC. OJ L 97, 12.4.2011, p. 38–40.
[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.
[4] Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 1–186.
[5] Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 187–188.

17 January 2020. In addition, an expert consultation in the area of mammalian toxicology was considered necessary.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the confirmatory data submitted in relation to the nature of residues in processed products and the toxicological assessment of the processing metabolites. A key supporting document to this conclusion is the peer review report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the compilation of comments in the reporting table to the conclusion. The peer review report (EFSA, 2020) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the reporting table (September 2015),
- the comments received on the revised addendum,
- the comments received on the draft EFSA conclusion (September–October 2015),
- the comments received on the second addendum to the draft assessment report,
- the comments received on the draft EFSA conclusion (May–June 2020).

Given the importance of the addendum to the assessment report (Greece, 2020) and the peer review report, these documents are considered as background documents to this conclusion.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated to have regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Dithianon is the ISO common name for 5,10-dihydro-5,10-dioxonaphtho[2,3-*b*]-1,4-dithiine-2,3-dicarbonitrile (IUPAC).

The representative formulated product for the evaluation was 'Delan 70 WG', a water dispersible granule (WG), containing 700 g/kg dithianon, registered under different trade names in Europe.

The representative uses evaluated comprise foliar spraying on table and wine grapes and pome fruit against various fungal diseases. Full details of the GAP can be found in the list of end points in Appendix A.

Conclusions of the evaluation (2015, 2020)

In the EFSA conclusion (EFSA, 2015), genotoxicity studies were provided on metabolites Reg. No. 31062, 4110904 and 4110933 indicating that these compounds are unlikely to be genotoxic. Metabolites Reg. No. 4005234 (Phthalic acid), Reg. No. 31062, Reg. No. 4107273 and Reg. No. 4110933 were found to be potentially relevant in processed commodities. Pending the outcome of the investigation on the magnitude of residues of these compounds in processed commodities, toxicological data would be needed to address the genotoxicity profile of metabolites Reg. No. 4005234 and Reg. No. 4107273 and the toxicity profile of the identified metabolites recovered at significant levels in processing studies.

Given the data gaps identified for storage stability data on dithianon residues in grape wine, and for the magnitude of the metabolites Reg. No. 4107273, Reg. No. 31062, Reg. No. 4005234 (phthalic acid) and Reg. No. 4110933 in apple and grapes processed commodities, the consumer exposure assessment could not be concluded on and this was identified as a critical area of concern. An acute intake concern has already been identified for table grapes (149% ARfD) in the previous EFSA conclusion.

In the meantime, the applicant conducted additional studies, in which the RMS has evaluated in a second addendum to the draft assessment report (Greece, 2020). The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the confirmatory data submitted in relation to the nature and magnitude of residues in processed products and the toxicological assessment of the processing metabolites.

Confirmatory data on mammalian toxicity

The toxicological profile of metabolites 1,4-naphthoquinone (Reg. No. 4107273), phthalic acid (Reg. No. 4005234), Reg. No. 4110904, Reg. No. 31062 and Reg. No. 4110933 was discussed at the Pesticides Peer Review Expert's meeting 25 in March 2020. New toxicological data submitted for all dithianon's metabolites were taken into consideration in the Addendum 2 to the draft assessment

report (Greece, 2020). During the meeting, the experts discussed about the grouping of metabolites, the genotoxicity potential, the general toxicity and the setting of reference values. The grouping was not considered appropriate as all these metabolites were regarded as dissimilar to the parent compound and among them according to a structural similarity analysis.

Genotoxic potential

For 1,4-naphthoquinone (Reg. No. 4107273), the conclusion on the genotoxicity potential was based in the *in vitro* and *in vivo* genotoxicity assays and systematic literature search included in the Addendum 2 to DAR (Greece, 2020). Applying a weight-of-evidence approach, it was concluded by the slight majority of experts that 1,4-naphthoquinone is unlikely to be genotoxic.[6] Some experts commented that the results are equivocal and not sufficient to disregard the positive *in vitro* results. It was also commented whether the bone marrow is the appropriate organ for follow up the positive *in vitro* assays. EFSA commented that looking at the *in vitro* results (positive in the presence of metabolic activation in one *in vitro* micronucleus, and positive in the presence and absence of S9 in another study), the bone marrow could be considered an appropriate tissue.

Regarding metabolite phthalic acid (Reg. No.4005234), the genotoxicity potential was mainly evaluated through an open literature search. In addition, an *in vitro* mammalian cell gene mutation test with phthalic anhydride was also available. It was concluded by the experts that phthalic acid is unlikely to be genotoxic.

Additional studies were not provided on metabolites Reg. No. 4110904, 31062 and 4110933. According to public literature data studies previously submitted on Reg No 4110904, 31062 and 4110933 in Addendum to DAR (Greece, 2014), it was agreed that these compounds are unlikely to be genotoxic.

General toxicity

For 1,4-naphthoquinone (Reg. No. 4107273), the literature search conducted by the applicant provided limited data on the systemic toxicity of the metabolite. Concerning the metabolite phthalic acid (Reg. No. 4005234), a systematic literature research was also provided by the applicant. It was concluded that phthalic acid is unlikely to be neurotoxic. However, the available data were not sufficient to derive specific toxicological reference values for both metabolites.

The use of the TTC approach to perform the consumer dietary risk assessment in regard to these metabolites was suggested by the applicant and the RMS in the addendum 2 to the Draft Assessment Report and proposed during the Pesticide Peer Review Meeting 25 (March 2020). However, the TTC approach as proposed in the EFSA PPR Guidance on the Residue Definition for risk assessment (EFSA PPR Panel, 2016) has not been endorsed by the Commission and the Member States. In view of these considerations, the TTC approach cannot be applied in this context. Based on the assessment given in the residue section, it is not required to provide further data to address the general toxicity of metabolites Reg. No 31062, Reg. No 4110904 and Reg. No 4110933. To conclude, a data gap is set regarding the general toxicity potential of metabolites 1,4-naphthoquinone (Reg. No. 4107273) and phthalic acid (Reg. No.4005234) as a complete consumer dietary risk assessment cannot be finalised.

Confirmatory data on storage stability

The submitted data demonstrated stability of dithianon residues under frozen conditions in apples for up to 24 months. Storage stability data on incurred residues of dithianon in grape wine were not provided. Although the processing studies demonstrated that dithianon residues were not recovered above the limit of quantification (LOQ) (0.01 mg/kg) in grape wine, the time interval between sampling and analysis ranged between 14 and 22 days from the processing trials and a fast degradation of the residues in grape wine samples cannot be excluded in view of the results of the previous storage stability data (recoveries < 10% within 1 month). EFSA noted that storage stability data on dithianon residues in grape wine and covering the maximum storage time interval of the samples from the processing residue trials were not submitted in the Addendum 2 to the draft assessment report (Greece, 2020).

[6] Refer to experts' consultation 2.1 in the Report of Pesticides Peer Review Experts' Meeting 25 (EFSA, 2020).

Confirmatory data on the nature and magnitude of residues in processed commodities

A processing study was submitted to address the nature of dithianon residues in processed commodities under hydrolysis conditions simulating the standard processing operations of pasteurisation, baking/brewing/boiling and sterilisation in apple juice. Dithianon was the predominant compound of the total applied radioactivity (TAR) for pasteurisation (up to 47.3% TAR) whilst it was extensively degraded for the two other processes into Reg. No. 4107273 (up to 12.7% TAR), Reg. No. 4110904 (up to 9.4% TAR), Reg. No. 31062 (up to 10.5% TAR) and to a lesser extent into Reg. No. 4005234 (Phthalic acid) and Reg. No. 4110933 (up to 2.2% and 4.1% TAR, respectively). Processing residue trials on apples and grapes determined the residue levels of dithianon and metabolites Reg. No. 4110904, Reg. No. 4107273, Reg. No. 31062, Reg. No. 4005234 (Phthalic acid) and Reg. No. 4110933 in processed commodities. These metabolites were determined according to analytical methods validated at an LOQ of 0.01 mg/kg for Reg. No. 4110904, Reg. No. 31062 and Reg. No. 4110933, at an LOQ of 0.1 mg/kg for Reg. No. 4107273 and at an LOQ of 1 mg/kg for Reg. No. 4005234 (Phthalic acid). Justifications to validate the analytical methods for the determination of residues of Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) at such high LOQs of 0.1 mg/kg and 1 mg/kg, respectively, were provided and considered as acceptable. None of these metabolites were quantified in raw apples and grapes fruits. Quantifiable residues of Reg. No. 4110904, Reg. No. 31062 and Reg. No. 4110933 were recovered in dried apples, apples dried pomace, pasteurised grape juice (rose) and in raisins but at significantly lower levels compared to the residue levels of dithianon in the respective matrices. These metabolites were never detected in the processed commodities of apples (juice, wet pomace) and of grapes (pasteurized juice (red), wine) that contribute significantly to the consumer and livestock dietary burden. Considering also the fact that their genotoxic potential could be ruled out (see Section 2), it can reasonably be concluded that a consumer dietary risk assessment in regard to these metabolites found in the apples and grapes processed commodities is not required and further data to address their general toxicity are not needed. Currently, no conclusion can be drawn on the relevance of metabolite Reg. No. 4107273 as this compound was determined in all apples and grapes processed matrices at a level below the LOQ of 0.1 mg/kg. EFSA is therefore of the opinion that the general toxicity of this compound should be provided (data gap in section 2). Regarding the metabolite Reg. No. 4005234 (Phthalic acid), significant residue levels in apples and grapes processed matrices cannot be excluded from the processing trials. Residue levels of phthalic acid were found below the LOQ of 1 mg/kg in all apples processed matrices whilst it accounted for levels up to 1.7 mg/kg in pasteurised grapes juice, 2 mg/kg in grape wine and 13 mg/kg in raisins. Considering the ubiquitous occurrence of phthalic acid and the fact that the background levels of this compound vs. the actual contribution from residue levels in processed matrices and resulting from dithianon treatment could not be provided, a data gap is set to address the general toxicity of Reg. No. 4005234 (Phthalic acid) (data gap in section 2). For the time being, the residue definitions for monitoring and risk assessment remain open for processed commodities and the consumer dietary risk assessment cannot be finalised. Furthermore, the data gap identified for storage stability data on dithianon residues in grape wine was not addressed. Considering the residue levels of dithianon in apples and table and wine grapes from the respective GAP-compliant residue trials and the toxicological reference values derived for dithianon, a provisional chronic and acute dietary intake calculation has been performed. An acute intake concern has already been identified for table grapes in the previous EFSA conclusions according to PRIMo rev.2A (IESTI: 149% ARfD). According to EFSA_PRIMo_rev.3.1 Model, a chronic intake concern was identified for the representative uses on pome fruit and table and wine grapes (IEDI: 109% acceptable daily intake (ADI) (NL toddler)) whilst an acute intake concern was confirmed for table grapes (IESTI: 165% ARfD) and was further identified for pears (IESTI: 118% ARfD).

Data gaps

This is a list of data gaps identified in the focussed peer review process of confirmatory data. Data gaps identified in the previously finalised EFSA conclusion on this active substance (EFSA, 2010) that were not part of the focussed peer review process of confirmatory data remain unchanged.

- The general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (phthalic acid) recovered at significant levels in apples and grapes processed commodities (relevant for all representative uses).

- Storage stability data on dithianon residues in grape wine and covering the maximum storage time interval of the samples from the processing residue trials (relevant for the representative use on wine grapes).

Concerns

1. Issues that could not be finalised

An issue is listed as an issue that could not be finalised where there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the Uniform Principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[7], and where the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

1) The data gap identified for storage stability data on dithianon residues in grape wine was not addressed. Given also the identified data gap to address the general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) recovered at significant levels in apples and grapes processed commodities, the residue definition for monitoring and risk assessment in processed commodities remain open and the consumer dietary risk assessment cannot be finalised.

2. Critical areas of concern

An issue is listed as a critical area of concern where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and where this assessment does not permit to conclude that for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment.

2) An acute intake concern has already been identified for table grapes (149% ARfD) in the previous EFSA conclusions according to PRIMo rev.2A. According to EFSA_PRIMo_rev.3.1 Model, a chronic intake concern was identified for the representative uses on pome fruit and table and wine grapes (IEDI: 109% ADI (NL toddler)) whilst an acute intake concern was confirmed for table grapes (IESTI: 165% ARfD) and was further identified for pears (IESTI: 118% ARfD).

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

Table 1: Overview of concerns

Representative use		Table grapes	Wine grapes	Pome fruit
Consumer risk	Risk identified	X^2	X^2	X^2
	Assessment not finalised	X^1	X^1	X^1

Columns are grey, if no safe use can be identified. The superscript number in this table relates to the numbered points indicated in Sections 1 and 2.

[7] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

References

EFSA (European Food Safety Authority), 2010. Conclusion on the peer review of the pesticide risk assessment of the active substance dithianon. EFSA Journal 2010;8(11):1904, 121 pp. https://doi.org/10.2903/j.efsa.2010.1904

EFSA (European Food Safety Authority), 2015. Conclusion on the peer review of the pesticide risk assessment for the active substance dithianon in light of confirmatory data. EFSA Journal 2015;13(11):4278, 20 pp. https://doi.org/10.2903/j.efsa.2015.4278

EFSA (European Food Safety Authority), 2020. Peer review report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance dithianon. Available online: www.efsa.europa.eu

EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2016. Guidance on the establishment of the residue definition for dietary risk assessment. EFSA Journal 2016;14(12):4549, 129 pp. https://doi.org/10.2903/j.efsa.2016.4549

European Commission, 2011. Guidance document on the procedures for submission and assessment of confirmatory data following inclusion of an active substance in Annex I of Council Directive 91/414/EEC. SANCO 5634/2009-rev. 4.5.

Greece, 2014. Addendum to the Draft Assessment Report (DAR) on the active substance dithianon prepared by the rapporteur Member State Greece in the framework of Directive 91/414/EEC, November 2013, revised in June 2014.

Greece, 2020. Addendum 2 to the Draft Assessment Report (DAR) on the active substance dithianon prepared by the rapporteur Member State Greece in the framework of Directive 91/414/EEC, September 2018, July 2019, revised in February 2020.

Abbreviations

a.s.	active substance
ADI	acceptable daily intake
AR	applied radioactivity
ARfD	acute reference dose
bw	body weight
DAR	draft assessment report
GAP	good agricultural practice
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LOQ	limit of quantification (determination)
MRL	maximum residue level
NEDI	National Estimate of Dietary Intake
NESTI	national estimated short-term intake
NEU	northern European Union
PHI	preharvest interval
SEU	southern European Union
STMR	supervised trials median residue
TAR	total applied radioactivity
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TTC	threshold of toxicological concern
VF	Variability factor
WG	water dispersible granule

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

Summary of representative uses evaluated

Crop and/or situation[a]	Member State, Country or Region	Product name	F G or I[b]	Pests or group of pests controlled[c]	Preparation		Application				Application rate per treatment (for explanation see the text in front of this section)			PHI (days)[m]	Remarks*
					Type[d],[e],[f]	Conc. of as[i]	Method kind[f],[g],[h]	Growth stage & season[j]	Number min/ max[k]	Interval between applications (min)	kg as/hL[l] min–max	Water L/ha min–max	kg as/ha[l] min–max		
Pome fruit	EU (South & North)	Delan 70 WG (BAS 216 03F)	F	*Venturia inaequalis, Gloeosporium spp.Nectria galligena Venturia pirina*	WG	700	High volume spraying	BBCH 10–79	1–12	7–12 days	0.0350–0.0525	1000–1500	0.525	21	Preventive treatment
Grape (Table and Wine)	EU (South & North)	Delan 70 WG (BAS 216 03F)	F	*Plasmopara viticola*	WG	700	High volume spraying	BBCH 10–79	1–8	7–12 days	0.047–0.140	400–1200	0.560	42	Preventive treatment Water volume is depending on the cropping

*: For uses where the column 'Remarks' is marked in grey further consideration is necessary.
Uses should be crossed out when the notifier no longer supports this use(s).
(a): For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g. fumigation of a structure).
(b): Outdoor or field use (F), greenhouse application (G) or indoor application (I).
(c): E.g. biting and suckling insects, soil born insects, foliar fungi, weeds.
(d): E.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR).
(e): GCPF Codes – GIFAP Technical Monograph No 2, 1989.
(f): All abbreviations used must be explained.
(g): Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench.
(h): Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plant type of equipment used must be indicated.
(i): g/kg or g/L. Normally the rate should be given for the active substance (according to ISO) and not for the variant in order to compare the rate for same active substances used in different variants (e.g. fluoroxypyr). **In certain cases, where only one variant is synthesised, it is more appropriate to give the rate for the variant (e.g. benthiavalicarb-isopropyl).**
(j): Growth stage at 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.

(k): Indicate the minimum and maximum number of application possible under practical conditions of use.
(l): The values should be given in g or kg whatever gives the more manageable number (e.g. 200 kg/ha instead of 200,000 g/ha or 12.5 g/ha instead of 0.0125 kg/ha.
(m): PHI – minimum preharvest interval.

Impact on Human and Animal Health

Other toxicological studies (Annex IIA, point 5.8)

Studies performed on metabolites or impurities	**D4 (Reg. No. 31062)** Ames test: negative (-) *In vivo* mouse micronucleus: (-) Unlikely to be genotoxic No data to set specific references values **Reg. No. 4110904** Ames test: (-) *In vitro* Gene mutation in mammalian cells: (-) *In vitro* clastogenicity in mammalian cells: positive (+) *In vitro* clastogenicity in mammalian cells: inconclusive *In vivo* micronucleus: (-) *In vivo* Comet assay: (-) Unlikely to be genotoxic No data to set specific references values. **D8 (Reg. No. 4110933)** Ames test: (-) *In vivo* micronucleus: (-) Unlikely to be genotoxic No data to set specific references values. **o-phthalic acid (Reg. No. 4005234)** *common metabolite to picoxistrobin and phosmet* Survey of published literature (November 2000) Acute oral LD_{50}, rat: 7500-8400 mg/kg bw *In vitro* genotoxicity (Ames test & cytogenetic assay in CHO cells): (-) Dominant lethal test: questionable positive test result involving reduced male fertility and abnormal sperm morphology Non-carcinogenic in rats and mice according to NTP carcinogenicity programme Reduced foetal body weight and retarded ossification in rats at maternal toxic doses Unlikely to be genotoxic No sufficient data to set specific references values Data gap for general toxicity **1,4-naphthoquinone (Reg. No. 4107273)** Ames test: (-) *In vitro* micronucleus assay: (+) *In vitro* micronucleus assay: (+) *In vivo* micronucleus assay: (-) General toxicity: Systematic literature research (supplementary information) Unlikely to be genotoxic No sufficient data to set specific references values Data gap for general toxicity

Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Fruits (apples, oranges), leafy crop (spinach), wheat (cereals) via foliar treatment
Rotational crops	Not required since intended to be used in permanent crops (pome fruits and grapes)
Metabolism in rotational crops similar to metabolism in primary crops?	Not required since intended to be used in permanent crops (pome fruits and grapes)
Processed commodities	Dithianon was the predominant compound of the total applied radioactivity (TAR) for pasteurisation (up to 47.3% TAR) while it was extensively degraded at baking/brewing/boiling and sterilisation into Reg. No 4107273 (up to 12.7 % TAR), Reg. No 4110904 (up to 9.4% TAR), Reg. No 31062 (up to 10.5% TAR) and to a lesser exten tinto Reg. No 4005234 (Phthalic acid) and Reg. No 4110933 (up to 2.2% and 4.1% TAR, respectively). Data gap: The general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) recovered at significant levels in apples and grapes processed commodities is required
Residue pattern in processed commodities similar to residue pattern in raw commodities?	No
Plant residue definition for monitoring	Open for processed commodities
Plant residue definition for risk assessment	Open for processed commodities
Conversion factor (monitoring to risk assessment)	Open

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Goat, hen
Time needed to reach a plateau concentration in milk and eggs	Goat: 1–2 days Hen: >4 days (not relevant, since the target crops are not fed to poultry)
Animal residue definition for monitoring	Dithianon
Animal residue definition for risk assessment	Dithianon
Conversion factor (monitoring to risk assessment)	Not applicable
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes (log P_{ow} > 3)

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Not required since intended to be used in permanent crops (pome fruits and grapes)

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

–Pome fruit : Acceptable storage stability of dithianon incurred residues under frozen conditions in apples for up to 24 months –Grapes: Incurred dithianon residues in wine grapes were shown to be stable under frozen conditions for up to 14 months covering the storage time interval of the samples from the residue trials – Processed grapes products: Dithianon is stable under freezer storage conditions in grape must (24 months), grape juice (18 months), grape pomace (6 months). However, an almost complete and rapid degradation of dithianon residues was observed in grape wine (recovery rate below 10% within 1 month of storage) Data gap: Storage stability data on dithianon residues in grape wine was not addressed.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant	Poultry	Pig
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no – If yes, specify the level)	Yes 0.39 mg/kg (dairy) 1.12 mg/kg (beef)	No	No
Potential for accumulation (yes/no):	No	No	No
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	No	No	No
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle Liver Kidney Fat Milk Eggs	No cow feeding study conducted metabolism results indicate that the residues will be far below the LOQ (milk, tissues 0.01 mg/kg)	No hen feeding study conducted metabolism results indicate that the residues will be far below the LOQ (eggs, tissues: 0.01 mg/kg)	No pig feeding study conducted; metabolism in rat and ruminant similar, residues will be below 0.01 mg/kg (LOQ).

LOQ: limit of quantification.

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

	Northern or Mediterranean Region, field or glasshouse and any other useful information	Trials results relevant to the representative uses[a]	Recommendation/ comments	MRL estimated from trials according to the representative use	HR[c]	STMR[b]
Apples	Northern	0.36, 2 × 0.48, 0.62, 0.76, 1.5, 1.7, 1.89 mg/kg	Extrapolation to the whole pome fruit group	3.0 mg/kg(1)	1.89 mg/kg	0.62 mg/kg
Pears	Northern	0.19, 0.37, 0.39, 0.87 mg/kg				
Apples	Southern	0.43, 0.59, 0.86, 1.69, 1.73 mg/kg				
Grapes (Table and Wine)	Northern	0.57, 0.62, 0.62, 0.98, 1.01, 1.20, 1.27, 1.41, 1.91, 2.2, 2.65 mg/kg	–	3.0 mg/kg(1)	2.72 mg/kg	1.01 mg/kg
	Southern	0.38, 0.52, 0.59, 1.0, 1.1, 1.48, 2.72 mg/kg				

(a): Numbers of trials in which particular residue levels were reported e.g. 3 × < 0.01, 1 × 0.01, 6 × 0.02, 1 × 0.04, 1 × 0.08, 2 × 0.1, 2 × 0.15, 1 × 0.17.
(b): Supervised Trials Median Residue, i.e. the median residue level estimated on the basis of supervised trials relating to the representative use.
(c): Highest residue.

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)(1)

ADI	0.01 mg/kg bw per day
TMDI (% ADI) according to EFSA PRIMo Model rev.2A	419.4% ADI (German child)
TMDI (% ADI) according to EFSA PRIMo Model rev.3.1	500% ADI (NL toddler)
NEDI (specify diet) (% ADI)	91.6% ADI (DE child)
IEDI (% ADI) according to EFSA PRIMo Model rev.3.1	109% ADI (NL toddler)
ARfD	0.12 mg/kg bw
IESTI (% ARfD) according to EFSA PRIMo Model rev.2A	Apples: 89.4% ARfD Pears: 79% ARfD Table grapes: 148.4% ARfD Wine grapes: 17.6% ARfD
IESTI (% ARfD) according to EFSA PRIMo Model rev.3.1	Table grapes: 165% ARfD Pears: 118% ARfD Apples: 96% ARfD Quinces:29% ARfD Medlar:13% ARfD Wine grapes: 21% ARfD
Factors included in IESTI	Factors included in IESTI calculation: – The NEU and SEU residue data set in pome fruit and grapes were respectively pooled as statistically supported. – Pome fruit: HR:1.89 mg/kg; VF: 3.8 (derived from the unit-to-unit variability residue study in apples) –Table/wine grapes: HR:2.72 mg/kg

ADI: acceptable daily intake; bw: body weight; TMDI: theoretical maximum daily intake; NEDI: National Estimate of Dietary Intake; IEDI: international estimated daily intake; IESTI: international estimated short-term intake: NEU: northern European Union; SEU: southern European Union; HR: highest residue; VF: Variability factor .

(1) The data gap identified for storage stability data on dithianon residues in grape wine was not addressed. Given also the identified data gap to address the general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) recovered at significant levels in apples and grapes processed commodities, the residue definition for monitoring and risk assessment in processed commodities remain open and the consumer dietary risk assessment cannot be finalised.

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)(1)

Crop/process/processed product	Number of studies	Processing factors		Amount transferred (%) (optional)
		Transfer factor	Yield factor	
Apple/washed apples	10 trials	0.23–1.8		
Apple/juice	13 trials	0.0045–0.1		
Apple/wet pomace	13 trials	0.49–3.5		
Apple/dry pomace	9 trials	0.43–1.35		
Apple/sauce	11 trials	0.006–0.125		
Apple/dried apples	5 trials	0.029, 2.18		
Apple/canned apples	7 trials	0.033–0.125		
Grapes/must	16 trials	0.01–0.39		
Grapes/wine	16 trials	0.002–0.08		
Grapes/juice	7 trials	0.002–0.003		
Grapes/wet pomace	7 trials	0.06–2.18		
Grapes/dry pomace	4 trials	0.08–0.28		
Grapes/young wine	7 trials	0.002–0.003		
Grapes/must deposit	1 trial	1.2		
Grapes/lees	2 trials	0.002, 0.01		

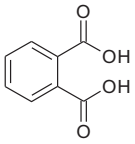
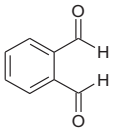
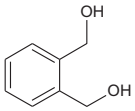
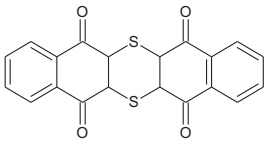
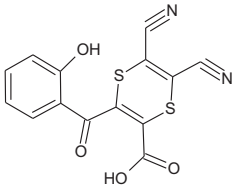
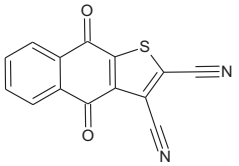
Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Pome fruits:	3.0 mg/kg(1),(2)
Wine grapes:	3.0 mg/kg(1),(2)

(1): The data gap identified for storage stability data on dithianon residues in grape wine was not addressed. Given also the identified data gap to address the general toxicity of metabolites Reg. No. 4107273 and Reg. No. 4005234 (Phthalic acid) recovered at significant levels in apples and grapes processed commodities, the residue definition for monitoring and risk assessment in processed commodities remain open and the consumer dietary risk assessment cannot be finalised.

(2): An acute intake concern has already been identified for table grapes (149% ARfD) in the previous EFSA conclusions according to PRIMo rev.2A. According to EFSA_PRIMo_rev.3.1 Model, a chronic intake concern was identified for the representative uses on pome fruit and table and wine grapes (IEDI: 109% ADI (NL toddler)) whilst an acute intake concern was confirmed for table grapes (IESTI: 165% ARfD) and was further identified for pears (IESTI: 118% ARfD).

Appendix B – Used compound codes

Code/trivial name	Chemical name/SMILES notation	Structural formula
phthalic acid **o-phthalic acid** **Reg. No 4005234**	phthalic acid OC(=O)c1ccccc1C(=O)O	
phthalaldehyde	phthalaldehyde O=Cc1ccccc1C=O	
1,2-benzenedimethanol	1,2-phenylenedimethanol OCc1ccccc1CO	
D4 **Reg. No. 31062**	5a,6a,12a,13a-tetrahydrodibenzo[*b*,*i*]thianthrene-5,7,12,14-tetrone O=C2C1SC5C(SC1C(=O)c3ccccc23)C(=O)c4ccccc4C5=O	
Reg. No. 4110904 **CL 1017911**	5,6-dicyano-3-(2-hydroxybenzoyl)-1,4-dithiine-2-carboxylic acid OC(=O)C=2SC(C#N)=C(SC=2C(=O)c1ccccc1O)C#N	
D8 **Reg. No. 4110933**	4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene-2,3-dicarbonitrile N#Cc1sc3c(c1C#N)C(=O)c2ccccc2C3=O	
D2 **Reg. No. 4107273**	1,4-naphthoquinone O=C2C=CC(=O)c1ccccc12