Setting of an import tolerance for fenazaquin in almonds

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Abstract

In accordance with Article 6 of Regulation (EC) No 396/2005, the applicant Gowan Crop Protection Ltd submitted a request to the competent national authority in Greece to set an import tolerance for the active substance fenazaquin in almonds. The data submitted in support of the request were found to be sufficient to derive a maximum residue level (MRL) proposal for almonds. Adequate analytical methods for enforcement are available to control the residues of fenazaquin and its metabolites on the commodities under consideration at the validated limit of quantification (LOQ) of 0.01 mg/kg. Based on the risk assessment results, EFSA concluded that the short-term and long-term intake of residues resulting from the use fenazaquin according to the reported agricultural practices is unlikely to present a risk to European consumers. The chronic consumer risk assessment is affected by non-standard uncertainties due to the lack of information on the occurrence of the metabolite 2-(4-tert-butylphenyl) ethanol (TBPE) in crops where the use of fenazaquin is the authorised in Europe. The reliable end points, appropriate for use in regulatory risk assessment are presented.

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Summary

In accordance with Article 6 of Regulation (EC) No 396/2005, Gowan Crop Protection Ltd submitted an application to the competent national authority in Greece (evaluating Member State (EMS)) to set an import tolerance for the active substance fenazaquin in almonds. The EMS drafted an evaluation report in accordance with Article 8 of Regulation (EC) No 396/2005, which was submitted to the European Commission and forwarded to the European Food Safety Authority (EFSA) on 25 January 2018. The EMS proposed to establish a maximum residue level (MRL) for almonds imported from the USA at the level of 0.02 mg/kg.

EFSA assessed the application and the evaluation report as required by Article 10 of the MRL regulation.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC and the additional data provided by the EMS in the framework of this application, the following conclusions are derived.

The metabolism of fenazaquin following foliar applications was sufficiently investigated in crops belonging to the fruit crops group.

Studies investigating the effect of processing on the nature of fenazaquin (hydrolysis studies) demonstrated that the fenazaquin is cleaved at the ether bridge in the molecule, leading to the degradation product quinazolin-4-ol (4-OHQ). Available studies do not investigate the fate of the phenyl ring moiety.

Investigations of residues in rotational crops are not required since almonds are a permanent crop and the MRL request concerns an import tolerance.

Based on the metabolic pattern identified in metabolism studies, hydrolysis studies, the toxicological significance of metabolites and degradation products, the residue definition for plant products proposed in the framework of the EU peer review was as fenazaquin (for enforcement); for risk assessment, fenazaquin and 2-(4-tert-butylphenyl) ethanol (TBPE) were considered relevant. Due to different mode of action of both substances and different toxicological reference values, a separate risk assessment was conducted for the two residue compounds.

EFSA concluded that for the crops assessed in this application, metabolism of fenazaquin in primary and the possible degradation in processed products has been sufficiently addressed and that the previously derived residue definitions are applicable.

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

The available residue trials are sufficient to derive a calculated MRL of 0.02 mg/kg for almonds.

Specific studies investigating the magnitude of fenazaquin residues in processed commodities are not required, as the residue concentrations expected in raw agricultural commodities (RAC) are low.

Residues of fenazaquin in commodities of animal origin were not assessed since the crop under consideration in this MRL application is normally not fed to livestock.

The toxicological profile of fenazaquin was assessed in the framework of the EU pesticides peer review under Directive 91/414/EEC and the data were sufficient to derive an acceptable daily intake (ADI) of 0.005 mg/kg body weight (bw) per day and an acute reference dose (ARfD) of 0.1 mg/kg bw. TBPE has been identified as the main metabolite and due to its toxicological relevance and different mode of action, toxicological reference values has been established for the metabolite. The ARfD and ADI of TBPE are 0.002 mg/kg bw (/day).

The consumer risk assessment was performed with revision 2 of the EFSA Pesticide Residues Intake Model (PRIMo). A separated consumer risk assessment has been performed for fenazaquin and for its metabolite TBPE. For fenazaquin, no long-term consumer intake concerns were identified for any of the European diets incorporated in the EFSA PRIMo. The total calculated intake accounted for 87.8% of the ADI (German, children), where the contribution of the residues in almonds to the total exposure accounting for 0.01% of ADI. No acute consumer risk was identified in relation to the MRL proposal for almonds; the highest calculated acute exposure was 0.04% of the ARfD.

In the absence of information on the concentration of TBPE in the crops for which authorised uses that exist in Europe, an indicative chronic exposure was calculated considering the existing MRLs according to Reg. No 833/2013, including several conservative assumptions, which introduce non-standard uncertainties in the dietary risk assessment for TBPE. Using the approach described in detail in section 3 of the document, a long-term risk to consumers from TBPE has not been identified. The
total calculated intake of TBPE accounted for 81.7% of the ADI (WHO Cluster diet B), where the contribution of the residues in almonds to the total exposure accounting for 0.02% of ADI. No acute consumer risk was identified for TBPE residues in almonds (1.2% of the ARfD).

EFSA concludes that residues resulting from the use of fenazaquin on almonds assessed in this reasoned opinion will not result in a consumer exposure exceeding the toxicological reference values of fenazaquin. However, the consumer risk assessment for TBPE is characterised by several uncertainties linked to the missing information on the levels of this metabolite associated to the existing authorised uses in Europe for which data are required. Information on the expected residue concentrations for metabolite TBPE should therefore be provided to EFSA to be assessed in the framework of the MRL review for fenazaquin under Article 12 of Regulation (EC) No 396/2005 which has been recently initiated.

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

| Code (a) | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|---------|-----------|-------------------------|-------------------------|-----------------------|
| 0120010 | Almonds   | 0.01*                   | 0.02                    | The submitted data are sufficient to derive a calculated MRL of 0.02 mg/kg for the import tolerance from USA. Residues in almonds related to the use of fenazaquin in accordance with the assessed GAP are not expected to pose a risk to EU consumers. |

MRL: maximum residue level; GAP: good agricultural practice.

*: Indicates that the MRL is set at the limit of analytical quantification (LOQ).
(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
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Assessment

The detailed description of the existing use of fenazaquin authorised in the USA in almonds, which is the basis for the current MRL application, is reported in Appendix A. Fenazaquin is the ISO common name for 4-tert-butylphenethyl quinazolin-4-yl ether (IUPAC). The chemical structures of the active substance and its main metabolites are reported in Appendix E.

Fenazaquin was evaluated in the framework of Directive 91/414/EEC1 with Greece designated as rapporteur Member State (RMS). The draft assessment report (DAR) prepared by the RMS has been peer reviewed by the European Food Safety Authority (EFSA, 2010b). Fenazaquin was approved2 for the use as an acaricide on ornamentals in greenhouses only on 1 June 2011. In 2011, Greece received an application for amendment to the conditions of approval of the active substance fenazaquin in the framework of Regulation (EC) No 1107/2009, in order to lift the restriction and allow uses on grapes and citrus (uses for which RMS previously applied for) as well as uses on pome fruit and stone fruit (additional uses) to be authorised. The addendum to the DAR prepared by the RMS under this framework has been peer reviewed by EFSA (2013).

The European Union (EU) maximum residue levels (MRLs) for fenazaquin are established in Annexes III of Regulation (EC) No 396/20053. The review of existing MRLs according to Article 12 of Regulation (EC) No 396/2005 (MRL review) is currently ongoing. A reasoned opinion on the modification of MRLs for fenazaquin in tea has been issued (EFSA, 2010a) and the proposals from this reasoned opinion have been considered in regulation4 for EU MRL legislation.

EFSA based its assessment on the evaluation report submitted by the EMS (Greece, 2018), the DAR and its addenda (Greece, 2006, 2010, 2012, 2013) prepared under Council Directive 91/414/EEC and in the framework of Regulation (EC) No 1107/20095 for amendment to the conditions of approval of fenazaquin, the Commission review report on fenazaquin (European Commission, 2011), the conclusions on the peer review of the pesticide risk assessment of the active substance fenazaquin (EFSA, 2010b, 2013), as well as the conclusions from a previous EFSA opinion on fenazaquin (EFSA, 2010a).

For this application, the data requirements established in Regulation (EU) No 544/20116 and the guidance documents applicable at the date of submission of the application to the EMS are applicable (European Commission, 1997a–g, 2000, 2010a,b, 2017; OECD, 2011). The assessment is performed in accordance with the legal provisions of the Uniform Principles for the Evaluation and the Authorisation of Plant Protection Products adopted by Commission Regulation (EU) No 546/20117.

As the review of the existing MRLs under Article 12 of Regulation 396/2005 is not yet finalised, the conclusions reported in this reasoned opinion should be taken as provisional and might need to be reconsidered in the light of the outcome of the MRL review.

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

The evaluation report submitted by the EMS (Greece, 2018) and the exposure calculations using the EFSA Pesticide Residues Intake Model (PRIMo) are considered as supporting documents to this reasoned opinion and, thus, are made publicly available as background documents to this reasoned opinion.

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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 Implementing Directive 2011/39/EU of 11 April 2011 amending Council Directive 91/414/EEC to include fenazaquin as active substance and amending Commission Decision 2008/934/EC. OJ L 97, 12.4.2011, p. 30–33.
3 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.
4 For an overview of all MRL Regulations on this active substance, please consult: http://ec.europa.eu/food/plant/pesticides/pesticides-database/public/?event=pesticide.residue.selection&language=EN
5 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.
6 Commission Regulation (EU) No 544/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the data requirements for active substances. OJ L 155, 11.6.2011, p. 1–66.
7 Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.
1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

Metabolism studies were evaluated at EU level in a previous reasoned opinion (EFSA, 2010a) and during the EU pesticide peer-review processes (EFSA, 2010b, 2013). Only a metabolism study in grapes was considered suitable to derive the residue definitions for enforcement and risk assessment. A major proportion of the total residue was present as parent fenazaquin. The levels of individual metabolites or fractions did not exceed 5% of the total radioactive residue (TRR) at harvest of the mature crop. There were indications of a cleavage of the fenazaquin molecule at the ether bridge that lead to the formation of quinazolin-4-ol (4-OHQ) and 2-(4-tert-butylphenyl) ethanol (TBPE).

1.1.2. Nature of residues in rotational crops

Metabolism data in rotational crops was not triggered during the peer review (representative uses on permanent crops only) and is not triggered by the current assessment since the MRL application is to accommodate an import tolerance from the USA.

1.1.3. Nature of residues in processed commodities

Standard hydrolysis studies evaluated during previous EFSA assessments (EFSA, 2010b, 2013) have shown that fenazaquin is highly degraded, leading to the formation of 4-OHQ under pasteurisation conditions. Since the fate of phenyl ring moiety was not investigated under simulated processing conditions, no information is available whether TBPE, the second cleavage product, will occur in significant amount in processed products or whether further degradation of this moiety is likely to occur.

Additional studies investigating the fate of the molecule under standard hydrolysis conditions would be desirable and should be provided in the framework of the MRL review. Considering the low residues expected in almonds and the low almond consumption, the additional uncertainty introduced to the risk assessment resulting from the lack of these study is considered acceptable (see also risk assessment approach used for TBPE).

1.1.4. Methods of analysis in plants

Analytical methods for the determination of fenazaquin and its residues in plant commodities were assessed in the framework of the peer review for amendment of approval conditions. EFSA concluded that adequate analytical methods are available to monitor residues of fenazaquin in high water, high oil and high acid content commodities and in starch/dry commodities at the limit of quantification (LOQ) of 0.01 mg/kg. Analytical methods are also available to monitor 4-OHQ and TBPE at 0.01 mg/kg in high acid and high water content commodities (EFSA, 2013).

Additional information has been provided in the framework of the current application that confirm the sufficiently validation of the existing analytical methods to monitor the residues of fenazaquin and its metabolites (TBPE and 4-OHQ) in almond nutmeat (high oil content commodities) (Greece, 2018).

1.1.5. Stability of residues in plants

Fenazaquin and its metabolites (TBPE, 4-OHQ) were found to be stable for 12 months under frozen conditions in high acid content matrices (orange, grapes) (EFSA, 2013). Storage stability information for high oil content matrices (almonds) has been submitted under the current MRL application (Greece, 2018) and residues of fenazaquin and its metabolites (TBPE and 4-OHQ) were found to be stable for 17 and 20 months respectively when stored under frozen condition at least in a minimum of −10°C.

1.1.6. Proposed residue definitions

Based on the available metabolism data in a crop from the same metabolism crop group that the one assess in the current MRL application and the existing toxicological characterisation of the active substance and its metabolites, the residue definitions applicable under the current MRL application only valid for the fruit crop group and processed commodities are as follows:
• Residue definition for enforcement: fenazaquin;
• Residue definition for risk assessment: fenazaquin and TBPE, considered separately.

Fenazaquin parent compound has been considered a good marker and was concluded for the enforcement residue definition, whereas the need to set a separate residue definition for risk assessment covering TBPE was based on toxicological considerations. Toxicological studies concluded that this metabolite is more toxic than the parent fenazaquin (EFSA, 2013).

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

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

In support of the MRL application, the applicant submitted eight residue trials performed in California during 2012 and 2014 in almond trees compliant with the USA good agricultural practice (GAP). In six out of the eight residue trials, the samples were analysed for fenazaquin and TBPE, while two trials that were analysed only for TBPE. Additionally, five GAP-compliant residue trials were submitted in which only the parent fenazaquin was analysed (Greece, 2018). Detailed information of the residue levels can be found in Table B.1.2.1. The data were sufficient to calculate a MRL proposal.

Considering that TBPE was not found in quantifiable concentrations in any of the trials in which TBPE was analysed, EFSA derived risk assessment values for TBPE in almonds at the LOQ of 0.01 mg/kg to be considered for exposure calculations.

The samples of these residue trials were stored under conditions for which integrity of the samples has been demonstrated (max. 12 months for fenazaquin and for a maximum of 20 months for its metabolites). Thus, the residue trials were considered valid with regard to the storage stability.

1.2.2. Magnitude of residues in rotational crops

Not triggered by the current assessment (see also Section 1.1.2).

1.2.3. Magnitude of residues in processed commodities

Not triggered by the current application. Specific studies to assess the magnitude of residues of fenazaquin and its residues during the processing of almonds are not considered necessary as the residue levels in RAC did not exceed the trigger value of 0.1 mg/kg (European Commission, 1997d).

1.2.4. Proposed MRLs

EFSA concludes that sufficient information was provided to calculate an MRL of 0.02 mg/kg in support of the import tolerance of almonds from the USA. In Section 3 of this Reasoned Opinion, the risk to consumers related to the calculated MRL is assessed.

2. Residues in livestock

No relevant for the current assessment.

3. Consumer risk assessment

The consumer risk assessment was performed with revision 2 of the EFSA PRIMo. The PRIMo model contains the relevant European food consumption data for different sub-groups of the EU population (EFSA, 2007). The exposure calculations were performed separately for fenazaquin and TBPE, assuming that the two compounds do not share a common mode of action.

The estimated exposure for fenazaquin and TBPE were then compared with the toxicological reference values derived for fenazaquin and its metabolite TBPE (EFSA, 2013).

As the MRL review of fenazaquin in accordance with Regulation (EC) No 396/2005 is ongoing, the conclusions reported in this reasoned opinion should be taken as provisional and should be reconsidered in the light of the outcome of the MRL review process.

The short-term exposure assessment has been performed using the highest residue (HR) for fenazaquin and TBPE observed in the supervised residue trials for almonds. No acute consumer risk was identified in relation to the MRL proposal for almonds, the highest calculated acute exposure
being less than 0.05% of the acute reference dose (ARfD) of fenazaquin and less than 2% of the ARfD of TBPE.

For the chronic risk assessment of fenazaquin, supervised trial median residues (STMR) were used for all those commodities previously assessed by EFSA, including the use in almond trees. For the other commodities, the existing MRLs set in Regulation (EU) No 893/2010 have been used for exposure calculations. The calculated exposure was then compared with the toxicological reference values as derived for fenazaquin (EFSA, 2013). No long-term consumer intake concerns were identified for any of the European diets incorporated in the EFSA PRIMo. The total calculated intake accounted for 87.8% of the acceptable daily intake (ADI; German, children), where the contribution of the residues in almonds to the total exposure accounting for 0.01% of ADI.

For the chronic risk assessment of TBPE, EFSA performed a conservative risk assessment screening, based on the STMR values derived for almonds and for previously assessed commodities. For the other crops, where the existing MRL is above the LOQ, TBPE residues relevant for consumer exposure might be expected. For those plant commodities, the existing MRLs for fenazaquin, multiplied by a molecular weight conversion factor were used to derive a conservative input value for the exposure calculation. Crops where the fenazaquin MRL is established at the LOQ and food of animal origin were excluded from this calculation, taking into account the TBPE was not observed in livestock metabolism studies. The underlying assumption is that residues of TBPE may be present at the level of the MRL (expressed as TBPE). The chronic exposure of TBPE did not exceed the ADI (81.7% of the ADI; WHO Cluster diet B) and the contribution of the residues in almonds to the total exposure accounting for 0.02% of ADI.

The input values used for the dietary exposure calculation are summarised in Appendix D and for further details on the exposure calculations, a screenshot of the Report sheet of the PRIMo is presented in Appendix C.

EFSA concludes that the proposed use of fenazaquin on almonds will not result in a consumer exposure exceeding the toxicological reference values of fenazaquin. However, EFSA emphasises that the consumer risk assessment for TBPE is characterised by several uncertainties linked to the missing information on the levels of this metabolite associated to the existing authorised uses in Europe for which data are required.

4. Conclusion and Recommendations

The data submitted in support of this MRL application were found to be sufficient to derive an MRL proposal for almonds.

EFSA concluded that the proposed use of fenazaquin in almonds is unlikely to pose a risk to consumers’ health; however, considering the high toxicity of the metabolite TBPE in comparison to fenazaquin and the lack of information in the current consumer exposure scenario for this metabolite according to the authorised uses in Europe, EFSA stresses the need for a revision of the existing authorised use in order to provide a refined risk assessment and guarantee that the MRLs in place do not pose a consumer health concern.

The MRL recommendation is summarised in Appendix B.4.

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8 Citrus fruits and grapes were assessed in the framework of the peer review as representative uses (EFSA, 2013). Since the existing EU MRL is identical with the MRL proposal derived in the peer review, the STMR values derived from the supervised field trials were considered realistic input values for the chronic risk assessment.

9 Commission Regulation (EU) No 893/2010 of 8 October 2010 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for acequinocyl, bentazon, carbendazim, cyfluthrin, fenamidone, fenazaquin, flonicamid, flutriafol, imidacloprid, ioxynil, metconazole, prothioconazole, prothioconazole and thiophanate-methyl in or on certain products. OJ L 266, 9.10.2010, p. 10–38.

10 MW fenazaquin: 306.4; MW TBPE: 178.3; MW correction factor 0.58 (178.3/306.4) applied to the existing MRLs above the LOQ.
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Abbreviations

4-OHQ quinazolin-4-ol
a.s. active substance
ADI acceptable daily intake
AR applied radioactivity
ARfD acute reference dose
BBCH growth stages of mono- and dicotyledonous plants
bw body weight
CF conversion factor for enforcement to risk assessment residue definition
DAR draft assessment report
DAT days after treatment
EMS evaluating Member State
FAO Food and Agriculture Organization of the United Nations
GAP Good Agricultural Practice
HPLC-MS/MS high performance liquid chromatography with tandem mass spectrometry
HR highest residue
IE DI international estimated daily intake
IESTI international estimated short-term intake
| Acronym | Definition |
|---------|------------|
| ILV     | independent laboratory validation |
| ISO     | International Organisation for Standardisation |
| IUPAC   | International Union of Pure and Applied Chemistry |
| LOQ     | limit of quantification |
| MRL     | maximum residue level |
| MW      | molecular weight |
| NEU     | northern Europe |
| OECD    | Organisation for Economic Co-operation and Development |
| PBI     | plant-back interval |
| PHI     | preharvest interval |
| PRIMO   | (EFSA) Pesticide Residues Intake Model |
| QuEChERS | Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method) |
| RA      | risk assessment |
| RAC     | raw agricultural commodity |
| RD      | residue definition |
| RMS     | rapporteur Member State |
| SANCO   | Directorate-General for Health and Consumers |
| SC      | suspension concentrate |
| SEU     | southern Europe |
| SMILES  | simplified molecular-input line-entry system |
| STMR    | supervised trials median residue |
| TBPE    | 2-(4-tert-butylphenyl) ethanol |
| TRR     | total radioactive residue |
| WHO     | World Health Organization |
### Appendix A – Summary of intended GAP triggering the amendment of existing EU MRLs

| Crop and/or situation | NEU, SEU, MS or country | F G or I<sup>(a)</sup> | Pests or Group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days) | Remarks |
|-----------------------|-------------------------|-----------------------|------------------------------------|-------------|-----------------------------|------------------------|-----------|---------|
| Almonds (0120000/TN 0660) | USA/Outdoor | F | Tetranychidae (mites) | SC 200 g/L Foliar spray | At infestation | 1 | n.a | 36–54 | 935 | 336–504 g a.s./ha | GWN-1708F (formulated product) may be tank mixed with non-ionic surfactants |

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

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

<sup>(b)</sup>: CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide formulation types and international coding system.

<sup>(c)</sup>: 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.

<sup>(d)</sup>: PHI: minimum preharvest interval.
## Appendix B – List of end points

### B.1. Residues in plants

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

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

| Primary crops (available studies) | Crop groups | Crop(s) | Application(s) | Sampling (DAT) | Comment/Source |
|-----------------------------------|-------------|---------|----------------|----------------|----------------|
| Fruit crops                       | Grapes      | F, 1 × 15 g/ha 2-3 weeks after BBCH 68 | 0, 46, 76 | Radiolabelled active substance: ¹⁴C-fenazaquin labelled in quinazoline (Q-fenazaquin) and in phenyl ring (P-fenazaquin) (EFSA, 2010a) |
| Fruit crops                       | Grapes      | F, 1 × 15 g/ha + 1 × 150 g/ha 9-10 weeks after BBCH 68 | 0, 28 | Radiolabelled active substance: ¹⁴C-fenazaquin labelled in quinazoline (Q-fenazaquin) and in phenyl ring (P-fenazaquin) (EFSA, 2010a) |

| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) | Comment/Source |
|--------------------------------------|-------------|---------|----------------|-----------|----------------|
| Not available and not triggered      |             |         |                |           |                |

| Processed commodities (hydrolysis study) | Conditions | Stable? | Comment/Source |
|-----------------------------------------|------------|---------|----------------|
| Pasteurisation (20 min, 90°C, pH 4)     | No         | Fenazaquin is significantly degraded to 4-OHQ particularly during pasteurisation (EFSA, 2013) |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | Inconclusive | – |
| Sterilisation (20 min, 120°C, pH 6)     | Inconclusive | – |
| Other processing conditions            | –          | –       |

Can a general residue definition be proposed for primary crops?  
No  
Only metabolism studies from fruit metabolism crop group investigated. (EFSA, 2013)

Rotational crop and primary crop metabolism similar?  
Not triggered  
Not triggered in the peer review (EFSA, 2013) and by the current application (Greece, 2018)

Residue pattern in processed commodities similar to residue pattern in raw commodities?  
Yes  
The nature of fenazaquin under standard hydrolysis conditions was only investigated in the quinazoline ring labelled fenazaquin.
Information on the occurrence of TPBE in processing commodities is not available. (EFSA, 2013)

| Fenazaquin (fruit crops only) |
|-----------------------------|

Fenazaquin (fruit crops only); TBPE (fruit crops only)
Separated risk assessment necessary due to the different toxicological properties of fenazaquin and TBPE.

Matrices with high acid content: multi-residue DFG method S19, HPLC-MS/MS, LOQ 0.01 mg/kg (fenazaquin, 4-OHQ)
Matrices with high water, high acid and high oil content and starch/dry commodities: QuEChERS method, HPLC-MS/MS, LOQ 0.01 mg/kg (fenazaquin)
Confirmatory method available.
ILV available. (EFSA, 2010a, 2013; Greece, 2018)

### B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category | Commodity | T (°C) | Stability period | Compounds covered | Comment/Source |
|-----------------------------------|----------|-----------|--------|-----------------|-------------------|----------------|
|                                   | High oil content | Almond nutmeat | –10 | 17 | Months | Fenazaquin, TBPE/4-OHQ | Temperatures range during storage between –10°C and –25°C Storage stability for TBPE/4-OHQ for 20 months (Greece, 2018) |
|                                   | High acid content | Oranges | –15 | 12 | Months | Fenazaquin | EFSA (2013) |
|                                   | High acid content | Orange pulp | – | 12 | Months | TBPE/4-OHQ | Storage temperatures reported as frozen conditions (EFSA, 2013) |
|                                   | Processed products | Raisins | – | 12 | Months | TBPE/4-OHQ | Storage temperatures reported as frozen conditions (EFSA, 2013) |

TBPE: 2-(4-tert-butylphenyl) ethanol; 4-OHQ: quinazolin-4-ol.
### B.1.2. Magnitude of residues in plants

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

| Commodity | Region/Indoor\(^{(a)}\) | Residue levels observed in the supervised residue trials (mg/kg) | Comments/Source | Calculated MRL (mg/kg) | HR\(^{(b)}\) (mg/kg) | STMR\(^{(c)}\) (mg/kg) | CF\(^{(d)}\) |
|-----------|--------------------------|---------------------------------------------------------------|-----------------|------------------------|-------------------|-------------------|---------|
| Almonds   | Import tolerance         | **Fenazaquin:** 9× < 0.01; 0.0155, 0.0155                     | Residue trials on almonds compliant with the US GAP        | **0.02**            | 0.0155            | 0.01              |         |
|           |                          | **TBPE:** 8 × < 0.01 mg/kg                                    |                 | –                      | 0.01              | 0.01              | –        |

MRL: maximum residue level; GAP: good agricultural practice; TBPE: 2-(4-tert-butylphenyl) ethanol.

\(^{(*)}\): Indicates that the MRL is proposed at the limit of quantification.

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

\(^{(b)}\): Highest residue according to the residue definition for risk assessment.

\(^{(c)}\): Supervised trials median residue according to the residue definition for risk assessment.

\(^{(d)}\): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.

*Underlined values show that the residue situation was more critical at longer PHI than the PHI for the GAP under assessment (PHI 21 days).
B.1.2.2. Residues in rotational crops

| | Not triggered | – |
| --- | --- | --- |

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

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

B.1.2.3. Processing factors

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

B.2. Residues in livestock

Not relevant for the current assessment.

B.3. Consumer risk assessment

| | Fenazaquin: 0.1 mg/kg bw (EFSA, 2013)  
TBPE: 0.002 mg/kg bw (EFSA, 2013) |
| --- | --- |

**ADI**

| | Fenazaquin: 0.005 mg/kg bw (EFSA, 2013)  
TBPE: 0.002 mg/kg bw (EFSA, 2013) |
| --- | --- |

**Highest IEDI, according to EFSA PRIMo**

Risk assessment results for fenazaquin

Risk assessment results for TBPE

Assumptions made for the calculations

Exposure calculation assumptions for fenazaquin

The calculation is based on the highest residue levels expected in the edible part (almonds nutmeat) of the raw agricultural commodities based on the GAP-complaint supervised residue trials submitted in support of this MRL application.

Exposure calculation assumptions for TBPE

The calculation was performed with the LOQ of 0.01 mg/kg considering that in none of the trials quantifiable residues of TBPE were found.

**ADI**

| | Fenazaquin: 0.005 mg/kg bw (EFSA, 2013)  
TBPE: 0.002 mg/kg bw (EFSA, 2013) |
| --- | --- |

**Highest IEDI, according to EFSA PRIMo**

Risk assessment results for fenazaquin

87.8% of ADI (German, children).

Contribution of crops assessed:

Almonds: 0.01% of ADI

Risk assessment results for TBPE

81.7% ADI (WHO Cluster diet B)

Contribution of crops assessed:

Almonds: 0.02 % of ADI
Assumptions made for the calculations

**Exposure calculation assumptions for fenazaquin**
The chronic exposure calculation is based on the median residue levels (STMR) derived for raw agricultural commodities based on the supervised residue trials and the MRLs set in Reg. (EU) No 893/2010. STMR values derived in the peer-review for which the MRL is the same that the MRL implemented in the Regulation has been used.

**Exposure calculation assumptions for TBPE**
For the chronic risk assessment of TBPE, a conservative screening risk assessment has been performed. STMR values derived for almonds and for previously assessed commodities have been used. For the other crops, where the existing MRL is above the LOQ, the existing MRLs for fenazaquin multiplied by a molecular weight conversion factor were used to derive a conservative input value for the exposure calculation. Crops where the fenazaquin MRL is established at the LOQ and food of animal origin were excluded from this calculation, taking into account the TBPE was not observed in livestock metabolism studies. The underlying assumption is that residues of TBPE may be present at the level of the MRL (expressed as TBPE). The conversion factor of 0.58 was derived as a quotient of the molecular weights of parent fenazaquin and the metabolite both substances (178.3/306.4).

### B.4. Recommended MRLs

| Code<sup>(a)</sup> | Commodity | Existing EU MRL (mg/kg) | Proposed EU MRL (mg/kg) | Comment/justification |
|-------------------|-----------|-------------------------|-------------------------|-----------------------|
| 0120010           | Almonds   | 0.01*                   | 0.02                    | The submitted data are sufficient to derive a calculated MRL of 0.02 mg/kg for the import tolerance from USA. Residues in almonds related to the use of fenazaquin in accordance with the assessed GAP are not expected to pose a risk to EU consumers |

**Enforcement residue definition:** fenazaquin

MRL: maximum residue level; GAP: good agricultural practice.

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

<sup>(a)</sup>: Commodity code number according to Annex I of Regulation (EC) No 396/2005.
Appendix C – Pesticide Residue Intake Model (PRIMo)

### Fenazaquin

| Status of the active substance: | 0.01 | Code no. | 0.01 |
|--------------------------------|------|---------|------|
| LOQ (mg/kg bw) | Proposed LOQ | | |

#### Toxicological endpoints

| ADI (mg/kg bw per day) | 0.005 | ARfD (mg/kg bw) | 0.1 |
|------------------------|-------|-----------------|-----|
| Source of ADI | EFSA | Source of ARfD | EFSA |
| Year of evaluation | 2013 | Year of evaluation | 2013 |

#### Chronic risk assessment – refined calculations

| Commodity/group of commodities | pTMRLs at LOQ (in % of ADI) |
|--------------------------------|-----------------------------|
| 87.8 DE child 24.1 12.9 9.8 Strawberries | 4.2 Peaches |
| 72.0 WHO Cluster diet B 30.8 5.0 4.2 Peaches | |
| 64.1 NL child 12.7 10.6 9.8 Bananas | 6.8 Bananas |
| 57.1 IE adult 10.5 5.7 4.6 Tomatoes | 5.0 Strawberries |
| 55.4 FR toddler 12.6 7.9 4.6 Sugar beet (root) | 7.7 Tomatoes |
| 41.6 UK Toddler 6.7 5.9 4.6 Tea (dried leaves and stalks) | 4.6 Tea (dried leaves and stalks) |
| 41.0 UK infant 7.7 5.8 4.0 Bananas | 7.7 Tomatoes |
| 37.8 ES child 9.8 7.4 3.3 Strawberries | 4.6 Tomatoes |
| 37.7 SE general population 90th percentile 7.7 7.2 | 7.7 Tomatoes |
| 36.8 DK child 6.5 5.3 5.0 Apples | |
| 36.1 FR infant 9.8 5.1 4.6 Apples | 4.3 Apples |
| 34.1 IT toddler/toddler 14.3 3.5 Peaches | 4.3 Apples |
| 33.3 WHO regional European diet 11.0 5.0 2.4 Strawberries | 4.3 apples |
| 29.1 WHO Cluster diet D 10.1 2.8 | 1.7 Strawberries |
| 28.1 IT adult 11.6 3.8 | 1.7 Strawberries |
| 28.0 WHO Cluster diet E 5.3 2.6 | 1.7 Strawberries |
| 27.7 PT General population 9.0 3.6 | 2.1 Peaches |
| 27.0 ES adult 7.8 4.4 | 2.1 Peaches |
| 24.4 WHO Cluster diet F 6.8 3.0 | 2.1 Peaches |
| 24.2 UK vegetarian 6.2 3.9 | 2.1 Peaches |
| 23.3 NL general 5.1 4.3 | 2.1 Peaches |
| 20.9 FR all population 4.3 3.2 | 2.1 Peaches |
| 19.9 PL general population 8.8 4.1 | 1.0 Plums |
| 19.3 UK adult 4.4 4.3 | 1.0 Plums |
| 17.6 DK adult 4.1 1.6 | 1.0 Plums |
| 17.0 FI adult 4.3 1.6 | 1.0 Plums |
| 16.6 LT adult 6.2 3.7 | 1.0 Plums |

### Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of Fenazaquin is unlikely to present a public health concern.
Setting of import tolerance for fenazaquin in almonds

**Acute risk assessment /children – refined calculations**

The acute risk assessment is based on the ARfD.

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

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

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

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

| Highest % of ARfD/ADI Commodities | pTMRL/ threshold MRL (mg/kg) | No of critical MRLs (IESTI 1) | No of critical MRLs (IESTI 2) |
|-----------------------------------|-------------------------------|-----------------------------|-----------------------------|
| Almonds                           | 0.036                         | ---                         | ---                         |
| Orange juice                      | 24.8                          | 0.5/-                       | ---                         |
| Peach juice                       | 9.0                           | 0.5/-                       | ---                         |
| Tomato juice                      | 8.7                           | 0.5/-                       | ---                         |
| Grape juice                       | 6.6                           | 0.2/-                       | ---                         |
| Apple juice                       | 5.1                           | 0.1/-                       | ---                         |

| Highest % of ARfD/ADI Commodities | pTMRL/ threshold MRL (mg/kg) | No of commodities for which ARfD/ADI is exceeded (IESTI 1): | No of commodities for which ARfD/ADI is exceeded (IESTI 2): |
|-----------------------------------|-------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Almonds                           | 0.036                         | ---                                                         | ---                                                         |
| Orange juice                      | 5.0                           | 0.5/-                                                       | ---                                                         |
| Peach juice                       | 1.0                           | Peach preserved with syrup                                  | ---                                                         |
| Tomato juice                      | 1.6                           | Tomato (preserved- 0.5/-                                   | ---                                                         |
| Grape juice                       | 0.8                           | Wine                                                        | ---                                                         |
| Apple juice                       | 0.7                           | Apple juice                                                 | ---                                                         |

**Conclusion:**

For Fenazaquin, IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.

No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

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

No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

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

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

| Highest % of ARfD/ADI Commodities | pTMRL/ threshold MRL (mg/kg) | No of commodities for which ARfD/ADI is exceeded (IESTI 1): | No of commodities for which ARfD/ADI is exceeded (IESTI 2): |
|-----------------------------------|-------------------------------|-------------------------------------------------------------|-------------------------------------------------------------|
| Almonds                           | 0.036                         | ---                                                         | ---                                                         |
| Orange juice                      | 24.8                          | 0.5/-                                                       | ---                                                         |
| Peach juice                       | 9.0                           | 0.5/-                                                       | ---                                                         |
| Tomato juice                      | 8.7                           | 0.5/-                                                       | ---                                                         |
| Grape juice                       | 6.6                           | 0.2/-                                                       | ---                                                         |
| Apple juice                       | 5.1                           | 0.1/-                                                       | ---                                                         |

**Conclusion:**

For Fenazaquin, IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.

No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

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

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

No exceedance of the ARfD/ADI was identified for any unprocessed commodity.

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*The results of the IESTI calculations are reported for at least 5 commodities. If the ARD is exceeded for more than 5 commodities, all IESTI values > 90% of ARD are reported.

***) pTMRL: provisional temporary MRL for unprocessed commodity.
Setting of import tolerance for fenazaquin in almonds

### TBPE

| Status of the active substance: | 0.01 |
|-------------------------------|------|
| LOQ (mg/kg bw)                | 0.01 |

**Toxicological end points**

| ADI (mg/kg bw per day): | 0.002 |
|-------------------------|-------|
| ARfD (mg/kg bw):        | 0.002 |

**Source of ADI:**

- EFSA

**Year of evaluation:**

- 2013

### Chronic risk assessment – refined calculations

#### TMDI values in % of ADI

| Commodity/group of commodities | 2nd contributor to MS diet (in % of ADI) | 3rd contributor to MS diet (in % of ADI) |
|-------------------------------|-----------------------------------------|-----------------------------------------|
| Tomatoes                      | 3.8                                     | 5.3                                     |
| Peaches                       |                                         |                                         |

#### pTMRLs at LOQ (in % of ADI)

| Commodity/group of commodities | 2nd contributor to MS diet (in % of ADI) | 3rd contributor to MS diet (in % of ADI) |
|-------------------------------|-----------------------------------------|-----------------------------------------|
| Peaches                       |                                         |                                         |
| Tomatoes                      |                                         |                                         |

### Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of TBPE is unlikely to present a public health concern.

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**Setting of import tolerance for fenazaquin in almonds**
### Setting of import tolerance for fenazaquin in almonds

**Acute risk assessment (children - refined calculations)**

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

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

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

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

| Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) |
|-----------------------------------|---------------------------|
| Almonds                           | 0.01/-                     |
| Orange juice                      | 0.50/0.04                  |
| Peach juice                       | 0.50/0.11                  |
| Tomato juice                      | 0.50/1.1                   |
| Grape juice                       | 0.20/0.06                  |
| Apple juice                       | 0.10/0.03                  |
| Plum juice                        | 0.30/0.14                  |

**No of critical MRLs (IESTI 1):** 6

**No of critical MRLs (IESTI 2):** 1

### Conclusion:

For TBPE IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.

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

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

For processed commodities, ARfD/ADI was exceeded in one or several cases.

**Processed commodities**

| Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) |
|-----------------------------------|---------------------------|
| Orange juice syrup                | 0.50/0.19                 |
| Tomato juice syrup                | 0.50/0.11                 |
| Tomato (preserved)                | 0.5/-                     |
| Wine                               | 0.2/-                     |
| Apple juice                       | 0.1/-                     |

**pTMRL:** provisional temporary MRL.

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

**Conclusion:**

For TBPE IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available. The estimated short term intake (IESTI 1) exceeded the ARfD/ADI for 0 commodities.

For processed commodities, the ARfD/ADI was exceeded in one or several cases.

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**No of commodities for which ARfD/ADI is exceeded (IESTI 1):** 6

**No of commodities for which ARfD/ADI is exceeded (IESTI 2):** 1
Appendix D – Input values for the exposure calculations

D.1. Consumer risk assessment for fenazaquin

| Commodity                      | Chronic risk assessment                          | Acute risk assessment                          |
|--------------------------------|--------------------------------------------------|-------------------------------------------------|
|                                | Input value (mg/kg) | Comment                                      | Input value (mg/kg) | Comment                                      |
| Almonds                        | 0.01               | STMR (Table B.1.2.1)                        | 0.0155             | HR (Table B.1.2.1)                          |
| Citrus fruits                  | 0.17               | STMR (EFSA, 2013)                           |                    |                                              |
| Grapes (table and wine grapes) | 0.04               | STMR (EFSA, 2013)                           |                    |                                              |
| Tea                            | 3.79<sup>(a)</sup> | STMR (EFSA, 2010a)                         |                    |                                              |
| All other commodities          | EU MRLs            | Reg. (EU) No 893/2010                       |                    |                                              |

STMR: supervised trials median residue; HR: highest residue.

<sup>(a)</sup>: Residues only for the parent compound fenazaquin were considered from being the only compound in the residue definition for risk assessment at that time (EFSA, 2010a).

D.2. Consumer risk assessment for TBPE metabolite

| Commodity                      | Chronic risk assessment                          | Acute risk assessment                          |
|--------------------------------|--------------------------------------------------|-------------------------------------------------|
|                                | Input value (mg/kg) | Comment                                      | Input value (mg/kg) | Comment                                      |
| Almonds                        | 0.01               | STMR (Table B.1.2.1)<sup>(a)</sup>            | 0.01               | HR (Table B.1.2.1)<sup>(a)</sup>              |
| Citrus fruits                  | 0.003              | STMR (EFSA, 2013)<sup>(b)</sup>               |                    |                                              |
| Grapes (table and wine grapes) | 0.01               | STMR (EFSA, 2013)<sup>(b)</sup>               |                    |                                              |
| Tea                            | 2.30               | STMR(EFSA, 2010a) × MW factor (0.58)<sup>(c)</sup> |                    |                                              |
| All plant origin commodities   | Several values     | Reg. (EU) No 893/2010See footnote<sup>(d)</sup>|                    |                                              |

TBPE: 2-(4-tert-butylphenyl) ethanol; STMR: supervised trials median residue; HR: highest residue; MRL: maximum residue level.

<sup>(a)</sup>: Residues of TBPE were not detected in the supervised residue trials submitted under the current application (Greece, 2018).

<sup>(b)</sup>: For those uses previously assessed (EFSA, 2013) and for which TBPE values were reported, the STMR values of TBPE were used for the chronic exposure calculation.

<sup>(c)</sup>: As mentioned in footnote (a), Table D.1. For the use of fenazaquin in tea (EFSA, 2010a), only fenazaquin was analysed as relevant compound. Considering that the median residue value is available from the supervised residue trials in tea, a conversion of residues by using the MW correction factor (0.58) was used in order to perform more refined exposure scenario.

<sup>(d)</sup>: Due to the lack of information of the occurrence of TBPE and the authorised used in Europe, where MRLs of fenazaquin are above the LOQ, a hypothetical residue situation where the MRL was converted into TBPE residues by multiplied the existing MRL by a molecular weight correction factor has been considered for exposure calculations. The MRLs at the LOQ (0.01 mg/kg) and the MRLs in food items of animal origin were not considered in the exposure calculation.
## Appendix E – Used compound codes

| Code/trivial name | IUPAC name/SMILES notation/InChiKey\(^{(a)}\) | Structural formula\(^{(b)}\) |
|------------------|---------------------------------------------|-----------------------------|
| Fenazaquin       | 4-tert-buty/phenethyl quinazolin-4-yl ether | ![Structural formula](image1) |
|                  | CC(C)(C)c1ccc(cc1)CCOc1ncnc2cccccc21       |                             |
|                  | DMYHGDADUDKCQ-UHFFFAOYSA-N                 |                             |
| TBPE             | 2-(4-tert-buty/phenyl)ethanol              | ![Structural formula](image2) |
|                  | CC(C)(C)c1ccc(CCO)cc1                     |                             |
|                  | NZGMMENPUKHODD-UHFFFAOYSA-N               |                             |
| 4-OHQ            | quinazolin-4-ol                           | ![Structural formula](image3) |
|                  | Oc1ncnc2cccccc21                          |                             |
|                  | QMNUDYFKZYBWQX-UHFFFAOYSA-N               |                             |

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system.

\(^{(a)}\): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).

\(^{(b)}\): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).