Review of the existing maximum residue levels for triazoxide according to Article 12 of Regulation (EC) No 396/2005

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Abstract

According to Article 12 of Regulation (EC) No 396/2005, EFSA has reviewed the maximum residue levels (MRLs) currently established at European level for the pesticide active substance triazoxide. To assess the occurrence of triazoxide residues in plants, processed commodities, rotational crops and livestock, EFSA considered the conclusions derived in the framework of Commission Regulation (EC) No 33/2008, as well as the European authorisations reported by Member States. Based on the assessment of the available data, MRL proposals were derived and a consumer risk assessment was carried out. All information required by the regulatory framework was present and a risk to consumers was not identified.

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Summary

Triazoxide was approved on 1 October 2011 by means of Commission Implementing Regulation (EU) No 807/2011 under Regulation (EC) No 1107/2009 as amended by Commission Implementing Regulations (EU) No 540/2011 and 541/2011.

As the active substance was approved after the entry into force of Regulation (EC) No 396/2005 on 2 September 2008, the European Food Safety Authority (EFSA) is required to provide a reasoned opinion on the review of the existing maximum residue levels (MRLs) for that active substance in compliance with Article 12(1) of the aforementioned regulation.

As the basis for the MRL review, on 16 November 2017, EFSA initiated the collection of data for this active substance. In a first step, Member States were invited to submit by 16 December 2017 their national Good Agricultural Practices (GAPs) in a standardised way, in the format of specific GAP forms, allowing the designated rapporteur Member State (RMS) Germany to identify the critical GAPs in the format of a specific GAP overview file. Only the RMS reported authorised GAPs which were fully supported by data. Therefore, Member States were not requested to provide residue data. On the basis of the feedback received by Member States and EU Reference Laboratories for Pesticides Residues (EURLs), EFSA asked the RMS to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report. The PROFile and evaluation report, including the Pesticide Residues Intake Model (PRIMO) calculations were provided by the RMS to EFSA on 10 April 2018. Subsequently, EFSA performed the completeness check of these documents with the RMS. The outcome of this exercise including the clarifications provided by the RMS, if any, was compiled in the completeness check.

Based on the information provided by the RMS, Member States and EURL, and taking into account the conclusions derived by EFSA in the framework of Commission Regulation (EC) No 33/2008, EFSA prepared in August 2018 a draft reasoned opinion, which was circulated to Member States for consultation via a written procedure. Comments received by 25 September 2018 were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

The metabolism of triazoxide in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement can be proposed as triazoxide, and for risk assessment as sum of triazoxide, M01 and M02, expressed as triazoxide. The effect of processing on residues was not investigated and is not required. Fully validated analytical methods are available for the enforcement of the proposed residue definition in high water, acid, oil and dry matrices at the limit of quantification (LOQ) of 0.001 mg/kg. According to the EURLs, the LOQ of 0.001 mg/kg for high water content and high acid content commodities and LOQ of 0.005 mg/kg for high oil content and dry commodities are achievable by using the QuEChERS method in routine analyses (EURLs, 2018).

Available residue trials data were considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation. Significant residue levels are not expected in succeeding crops provided that triazoxide is applied according to the current authorisations.

Triazoxide is authorised for use on crops that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance (OECD, 2013). Since the calculated dietary burdens for all groups of livestock were found to be below the trigger value of 0.1 mg/kg dry matter (DM), further investigation of residues as well as the setting of MRLs in commodities of animal origin is not necessary. A metabolism study in lactating goats at an exaggerated dose also confirmed that residues are not expected in commodities of animal origin.

Accordingly, the derivation of a residue definition for enforcement and risk assessment in livestock commodities is not necessary. Nonetheless, an analytical method for the detection of the parent compound at the LOQ of 0.001 mg/kg in all matrices is available.

Chronic and acute consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 2 of the EFSA PRIMO. The highest acute exposure amounted to 0.6% of the acute reference dose (ARF) (wheat) and the highest chronic exposure represented 31% of the acceptable daily intake (ADI) (Danish child).
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Review of the existing MRLs for triazoxide

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Background

Regulation (EC) No 396/2005\(^1\) (hereinafter referred to as 'the Regulation') establishes the rules governing the setting and the review of pesticide maximum residue levels (MRLs) at European level. Article 12(1) of that Regulation stipulates that the European Food Safety Authority (EFSA) shall provide, within 12 months from the date of the inclusion or non-inclusion of an active substance in Annex I to Directive 91/414/EEC\(^2\) a reasoned opinion on the review of the existing MRLs for that active substance.

As triazoxide was approved on 1 October 2011 by means of Commission Implementing Regulation (EU) No 807/2011\(^3\) under Regulation (EC) No 1107/2009\(^4\) as amended by Commission Implementing Regulations (EU) No 540/2011\(^5\) and 541/2011\(^6\), EFSA initiated the review of all existing MRLs for that active substance.

In accordance with Article 18 of Commission Regulation (EC) No 33/2008\(^7\), triazoxide was evaluated by the United Kingdom, designated as rapporteur Member State (RMS) in the resubmission procedure. Subsequently, a peer review on the initial evaluation of the RMS was conducted by EFSA, leading to the conclusions as set out in the EFSA scientific report (EFSA, 2011). The approval of triazoxide is restricted to uses as a fungicide for seed treatment.

According to the legal provisions, EFSA shall base its reasoned opinion in particular on the relevant assessment report prepared under Directive 91/414/EEC repealed by Regulation (EC) No 1107/2009.

To gain an overview of the pesticide residues data that have been considered for the setting of the existing MRLs, EFSA developed the Pesticide Residues Overview File (PROFile). The PROFile is an inventory of all pesticide residues data relevant to the risk assessment and MRL setting for a given active substance. This includes data on:

- the nature and magnitude of residues in primary crops;
- the nature and magnitude of residues in processed commodities;
- the nature and magnitude of residues in rotational crops;
- the nature and magnitude of residues in livestock commodities;
- the analytical methods for enforcement of the proposed MRLs.

As the basis for the MRL review, on 16 November 2017, EFSA initiated the collection of data for this active substance. In a first step, Member States were invited to submit by 16 December 2017 their Good Agricultural Practices (GAPs) that are authorised nationally, in a standardised way, in the format of specific GAP forms. In the framework of this consultation five Member States provided feedback on.
their national authorisations of triazoxide (the Czech Republic, Germany, Ireland, Lithuania and Sweden). Based on the GAP form submitted, no authorised uses for this active substance were reported except the ones submitted by the RMS. Only the RMS reported authorised GAPs in the overview file, which were fully supported by data. Therefore, Member States were not requested to provide residue data.

On the basis of all the data submitted by Member States and the EU Reference Laboratories for Pesticides Residues (EURL), EFSA asked Germany to complete the PROFile and to prepare a supporting evaluation report. The PROFile and the supporting evaluation report, together with the Pesticide Residues Intake Model (PRIMo) calculations, were submitted to EFSA on 10 April 2018. Subsequently, EFSA performed the completeness check of these documents with the RMS. The outcome of this exercise including the clarifications provided by the RMS, if any, was compiled in the completeness check report.

Considering all the available information, EFSA prepared in August 2018 a draft reasoned opinion, which was circulated to Member States for commenting via a written procedure. All comments received by 25 September 2018 were considered by EFSA during the finalisation of the reasoned opinion.

The evaluation report submitted by the RMS (Germany, 2018), taking into account also the information provided by Member States during the collection of data, and the EURL report on analytical methods (EURL, 2018) are considered as main supporting documents to this reasoned opinion and, thus, made publicly available.

In addition, further supporting documents to this reasoned opinion are the completeness check report (EFSA, 2018a) and the Member States consultation report (EFSA, 2018b). These reports are developed to address all issues raised in the course of the review, from the initial completeness check to the reasoned opinion. Furthermore, the exposure calculations for all crops reported in the framework of this review performed using the PRIMo and the PROFile as well as the GAP overview file listing all authorised uses are key supporting documents and made publicly available as background documents to this reasoned opinion. A screenshot of the report sheet of the PRIMo is presented in Appendix C.

Terms of Reference

According to Article 12 of Regulation (EC) No 396/2005, EFSA shall provide a reasoned opinion on:

- the inclusion of the active substance in Annex IV to the Regulation, when appropriate;
- the necessity of setting new MRLs for the active substance or deleting/modifying existing MRLs set out in Annex II or III of the Regulation;
- the inclusion of the recommended MRLs in Annex II or III to the Regulation;
- the setting of specific processing factors as referred to in Article 20(2) of the Regulation.

The active substance and its use pattern

Triazoxide is the ISO common name for 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine 1-oxide (IUPAC).

The chemical structure of the active substance and its main metabolites are reported in Appendix F. Triazoxide belongs to the class of imidazole fungicides, alternatively classified as a benzotriazine fungicide. It is a contact and non-systemic fungicide; target organisms are killed on contact with the fungicide, the exact mode of action is not known. Triazoxide is used in agriculture in cereals seed treatment, to control a range of fungal diseases.

Triazoxide was first evaluated in the framework of Directive 91/414/EEC with the United Kingdom designated as RMS. Following the Commission Decision 2009/860 concerning the non-inclusion of triazoxide in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, in accordance with Article 11(e) of Commission Regulation (EC) No 1490/2002 the applicant Bayer CropScience AG made a resubmission application.

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6 2009/860/EC: Commission Decision of 30 November 2009 concerning the non-inclusion of triazoxide in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance (notified under document C(2009) 9271) (Text with EEA relevance) OJ L 314, 1.12.2009, p. 81-82.

9 1490/2002/EC: Commission Regulation (EC) No 1490/2002 of 14 August 2002 laying down further detailed rules for the implementation of the third stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000. OJ L 224, 21.8.2002, p. 23-48.
for the inclusion of triazoxide in Annex I in accordance with the provisions laid down in Commission Regulation (EC) No 33/2008.

The applicant resubmission of the additional data via accelerated procedure (Regulation (EC) No 33/2008), was evaluated by the RMS in the format of an Additional Report of triazoxide (United Kingdom, 2011). The representative uses supported for the peer review process was as seed treatment on cereals acting as a fungicide. Following the peer review, which was carried out by EFSA (EFSA, 2011), a decision on inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Implementing Regulation 807/2011, which entered into force on 1 October 2011. According to Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011, triazoxide has been approved under Regulation (EC) No 1107/2009. This approval is restricted to uses as a fungicide for seed treatment only.

For triazoxide, a default MRL of 0.01 mg/kg is established according to Art 18 (1)(b) of Regulation (EC) No 396/2005. Codex maximum residue limits (CXLs) for triazoxide are not available. No MRL changes occurred since the entry into force of the Regulation mentioned above.

For the purpose of this MRL review, all the uses of triazoxide currently authorised within the EU as submitted by the Member States during the GAP collection, have been reported by the RMS in the GAP overview file. The critical GAPs identified in the GAP overview file were then summarised in the PROFile and considered in the assessment. The details of the authorised critical GAPs for triazoxide are given in Appendix A. No import tolerances were reported by the RMS.

Assessment

EFSA has based its assessment on the following documents:

- the PROFile submitted by the RMS;
- the evaluation report accompanying the PROFile (Germany, 2018);
- the draft assessment report (DAR) and its addenda prepared under Council Directive 91/414/EEC (United Kingdom, 2007);
- the additional report (AR) and its addenda prepared under Commission Regulation (EC) No 33/2008 (United Kingdom, 2011);
- the conclusion on the peer review of the pesticide risk assessment of the active substance triazoxide (EFSA, 2009, 2011);

The assessment is performed in accordance with the legal provisions of the uniform principles for evaluation and authorisation of plant protection products as set out in Commission Regulation (EU) No 546/201110 and the currently applicable guidance documents relevant for the consumer risk assessment of pesticide residues (European Commission, 1997a–g, 2000, 2010a,b, 2017; OECD, 2011, 2013).

More detailed information on the available data and on the conclusions derived by EFSA can be retrieved from the list of end points reported in Appendix B.

1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

The metabolism of triazoxide was investigated after seed treatment in cereals (United Kingdom, 2007, 2011) and assessed in the framework of the peer-review (EFSA, 2011). In the studies, triazoxide was radiolabelled in the phenyl ring of the molecule.

In the first metabolism study conducted on barley, the individual components were not identified, as low total radioactive residues (TRR) were observed at harvest in both grains and in straw (United Kingdom, 2007). However, given the very low acceptable daily intake (ADI) allocated to the parent and that the absence of residues could not be confirmed, due to an inappropriate limit of quantification (LOQ) of 0.05 mg/kg in the supervised trials, an additional metabolism study was requested (EFSA, 2009).

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10 546/2011/EU: 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.
In the second metabolism study, after seed application of 3 g and 30 g a.s./100 kg seeds on barley seeds TRRs were also low: 0.003 mg eq/kg in grain for both doses, and up to 0.013 mg/kg in straw. The higher seed application rate was already severely phytotoxic, with only a few seeds germinating. In view of the very low TRR in grain, individual residues were not identified. In straw following the higher application rate, out of the ~50% of the extractable radioactivity, triazoxide and its metabolites, M01 and M02 were identified at a rate of 2.1% (0.0004 mg/kg), 5.9% (0.0008 mg/kg) and 4% (0.0005 mg/kg) of the TRR, respectively. The remaining extracted radioactivity constituted of 15 unknown compounds, all below 6% of the TRR (EFSA, 2011). Based on the metabolic pathway observed in the study, it was concluded that the primary metabolism occurs in the imidazole ring. In the light of this and the very low TRR, in particular in grain, studies with imidazole ring labelled $^{14}$C triazoxide would not have an impact on the assessment and therefore are not required.

1.1.2. Nature of residues in rotational crops

Triazoxide is authorised on crops that may be grown in rotation. Triazoxide and its metabolites (M01 and M02) are highly or very highly persistent based on the field DT$_{90}$ (>365 days) reported in the soil degradation studies evaluated in the framework of the peer review (EFSA, 2011). The assessment of the peer-review covers the most critical GAPs assessed in the present review. A confined rotational crop study with triazoxide radiolabelled on the phenyl ring was assessed in the framework of the peer-review (EFSA, 2011). Clover and turnips were planted in soil 131 days after planting barley seeds treated with phenyl ring labelled $^{14}$C-triazoxide at an application rate of 19 g as/ha. At harvest, total residues were below 0.001 mg eq./kg. As total radioactivity was very low, further investigation of the identity of the components was not considered necessary.

As described above (see Section 1.1.1), triazoxide-treated barley seeds (3 and 30 g a.s./kg seed) were sown at a rate equivalent to 5.3 and 53 g a.s./ha. The most critical GAP has an application rate of 3.8 g a.s./ha. Crop samples were taken up to 136 days following sowing. The only metabolites that could be identified were M01 and M02, each below 0.001 mg/kg. Given the persistence of the parent and its two metabolites, M01 and M02, and the relatively high application rate of the seed treatment, it can be expected that triazoxide and its metabolites were present at sufficiently high concentration during the growing period, and primary plants were sufficiently exposed compared to cereals grown in rotation. Considering all aspects, it is considered that the exposure via the soil is sufficiently addressed, and the primary metabolism study in barley can be accepted as a surrogate for rotational crops.

Therefore, the conclusion of the peer-review is still applicable; the seed treatment of barley, as a pre-emergence treated crop can be accepted as a substitute for a third succeeding crop category (cereals). Given the very slow degradation of triazoxide and its metabolites in soil (see above), residue uptake are not expected to be higher within the first 131 days, and therefore further investigation at a plant-back interval of 30 days is not necessary. Overall, it can be concluded that residues in succeeding crops are not expected following seed treatment provided triazoxide is used according to the authorised GAPs.

1.1.3. Nature of residues in processed commodities

There were no studies investigating the nature of residues of triazoxide in processed commodities available for this review. However, given that in all commodities residues were below 0.001 mg/kg, and no residues are expected following the use of triazoxide according to the authorised GAPs, the investigation of the nature of residues in processed commodities is not required.

1.1.4. Methods of analysis in plants

During the peer-review, an analytical method based on high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS/MS) detection was fully validated in high water, high acid, high oil and dry matrices with a LOQ of 0.001 mg/kg, and in straw with a LOQ of 0.005 mg/kg (EFSA, 2011).

Additional information on the availability of analytical method for the enforcement of triazoxide during routine laboratory analyses was also provided by the EURLs in the framework of this review. According to the information received, by using a QuEChERS method, an LOQ of 0.001 mg/kg in high water content and high acid content commodities and an LOQ of 0.005 mg/kg for high oil content and dry commodities is achievable for routine analyses of triazoxide (EURLs, 2018).
1.1.5. Stability of residues in plants

The storage stability of triazoxide was investigated in the framework of the peer review (EFSA, 2011). In dry/high starch (grains) and high water (forage) content commodities, as well as straw, the available studies demonstrated storage stability for triazoxide for a period of 24 months when stored at –18°C.

1.1.6. Proposed residue definitions

Based on the metabolism of triazoxide, detectable amounts of residues, parent or its metabolites, are not expected in cereals when used according to the existing GAPs. Therefore, the residue definition for enforcement is proposed as triazoxide only; this proposal is limited to cereal commodities subject to seed treatment.

An analytical method for the enforcement of the proposed residue definition at the LOQ of 0.001 mg/kg in all four main plant matrices is available (EFSA, 2011). According to the EURLs, the LOQ of 0.001 or 0.005 mg/kg is achievable by using the QuEChERS method in routine analyses (EURL, 2018).

At PRAPeR 49 meeting on mammalian toxicology experts concluded that metabolites M01 and M02 should be considered of comparable toxicity to triazoxide. Given that these metabolites occurred at higher levels in forage and straw than the parent, they were included in the residue definition for risk assessment (EFSA, 2011). Therefore, the residue for risk assessment was defined as the sum of triazoxide and metabolites M01 and M02, expressed as triazoxide. For risk assessment, a conversion factor (CF) of 6 was proposed in the framework of the peer review, based on the respective proportions at which triazoxide (2.1%) and its metabolites, M01 (5.9%) and M02 (4%) were observed in straw (EFSA, 2011). These residue definitions and the conversion factor proposed during the peer review are deemed applicable for the present MRL review.

It is noted that in case additional uses on crops will be granted in the future, the proposed residue definitions may need to be reconsidered.

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

To assess the magnitude of triazoxide residues resulting from the reported GAPs, EFSA considered all the residue trials evaluated in the framework of the peer review (EFSA, 2011). No other trials were reported by the RMS in its evaluation report (Germany, 2018). All residue trial samples considered in this framework were stored in compliance with the conditions for which storage stability of residues was demonstrated. Decline of residues during storage of the trial samples is therefore not expected.

The number of residue trials and extrapolations were evaluated in accordance with the European guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs (European Commission, 2017).

Available residue trials are sufficient to derive MRL and risk assessment values, taking note of the following considerations:

- the occurrence of metabolites M01 and M02 was not investigated. However, as residues of triazoxide were below the detection limit of 0.001 mg/kg, a conversion factor of 6 based on the metabolism studies was used for risk assessment. It is noted that for cereal grains this CF is very conservative, as the TRR was 0.003 mg eq/kg even at 15N dose of the most critical use.
- the storage stability of triazoxide metabolites M01 and M02 were not investigated. However, as M01 and M02 residues were not analysed in the trials this has no impact on the present risk assessment.
- Barley, oat, rye, wheat: four residue trials are available supporting these GAPs. The reduced number of residue trials is considered acceptable, because all results were below the LOQ of 0.001 mg/kg, and a no residues situation is expected. Further residue trials are therefore not required.

1.2.2. Magnitude of residues in rotational crops

Based on the confined rotational crop studies and the magnitude of residues studies in primary crops as surrogate study for cereals (see Sections 1.1.2 and 1.2.1), it can be concluded that significant
residue levels are not expected in succeeding crops provided that triazoxide is applied according to the current authorisations reported in Appendix A.

1.2.3. Magnitude of residues in processed commodities

The effect of industrial processing and/or household preparation was not assessed and is not required as residues are not expected to be above the detection limit of 0.001 mg/kg.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation.

2. Residues in livestock

Triazoxide is authorised for use on cereals that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance (OECD, 2013), which has now also been agreed upon at European level. The input values for all relevant commodities are summarised in Appendix D. Since the calculated dietary burdens for all groups of livestock were found to be below the trigger value of 0.1 mg/kg dry matter (DM), further investigation of residues as well as the setting of MRLs in commodities of animal origin is normally not necessary.

Given the very low ADI for this active substance, the possible presence of residues in ruminant matrices was investigated in lactating goats. This study was assessed in the framework of the peer-review (EFSA, 2011).

Animals were dosed with 4.3 mg/kg DM 14C-phenyl-labelled triazoxide (2150N) for five consecutive days. The total radioactive residues were very low (< 0.01 mg/kg in fat up to 0.26 mg/kg in liver) and individual metabolites were not investigated. Considering the exaggerated dose rate it can be concluded that residues are not expected at significant levels in animal commodities. Therefore, the setting of a residue definition and proposing MRLs in animal products is not considered necessary.

Nonetheless, a fully validated analytical method is available; using HPLC-MS/MS for the determination of triazoxide in all animal tissues, milk and eggs, with a LOQ of 0.001 mg/kg (EFSA, 2011).

3. Consumer risk assessment

Chronic and acute exposure calculations for all crops reported in the framework of this review were performed using revision 2 of the EFSA PRIMo (EFSA, 2007). Input values for the exposure calculations were derived in compliance with the decision tree reported in Appendix E. Hence, for the commodities where a MRL could be derived by EFSA in the framework of this review, input values were derived according to the internationally agreed methodologies (FAO, 2009). All input values included in the exposure calculations are summarised in Appendix D.

The exposure values calculated were compared with the toxicological reference values for triazoxide, derived by EFSA (2011). The highest chronic exposure was calculated for the Danish child, representing 31% of the ADI, and the highest acute exposure was calculated for wheat, representing 0.6% of the acute reference dose (ARFD). These calculations indicate that the uses assessed under this review result in a consumer exposure lower than the toxicological reference values. Therefore, these uses are unlikely to pose a risk to consumer’s health.

It is noted that in the framework of the peer-review the possible presence of triazoxide and its metabolites M01 and M02 in groundwater was investigated (EFSA, 2011). It was concluded that the presence of these metabolites in groundwater is predicted to be very low (< 0.0001 μg/L) and the contribution of the residues in drinking water to consumer exposure insignificant (< 0.1% of ADI). In view of the representative use being more critical compared to the most critical authorised use, this conclusion remains applicable for the present MRL review.

Conclusions

The metabolism of triazoxide in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement can be proposed as triazoxide, and for risk assessment as sum of triazoxide, M01 and M02, expressed as triazoxide. The effect of processing on residues was not investigated and is not required. Fully validated analytical
Methods are available for the enforcement of the proposed residue definition in high water, acid, oil and dry matrices at the LOQ of 0.001 mg/kg. According to the EURLs, the LOQ of 0.001 mg/kg for high water content and high acid content commodities and LOQ of 0.005 mg/kg for high oil content and dry commodities are achievable by using the QuEChERS method in routine analyses (EURLs, 2018).

Available residue trials data were considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation. Significant residue levels are not expected in succeeding crops provided that triazoxide is applied according to the current authorisations.

Triazoxide is authorised for use on crops that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance. Since the calculated dietary burdens for all groups of livestock were found to be below the trigger value of 0.1 mg/kg DM, further investigation of residues as well as the setting of MRLs in commodities of animal origin is not necessary. A metabolism study in lactating goats at an exaggerated dose also confirmed that residues are not expected in commodities of animal origin.

Accordingly, the derivation of a residue definition for enforcement and risk assessment in livestock commodities is not necessary. Nonetheless, an analytical method for the detection of the parent compound at the LOQ of 0.001 mg/kg in all matrices is available.

Chronic and acute consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 2 of the EFSA PRIMo. The highest acute exposure amounted to 0.6% of the ARfD (wheat) and the highest chronic exposure represented 31% of the ADI (Danish child).

**Recommendations**

MRL recommendations were derived in compliance with the decision tree reported in Appendix E of the reasoned opinion (see Table 1). All MRL values listed in the table are sufficiently supported by data and are therefore proposed for inclusion in Annex II to the Regulation.

**Table 1:** Summary table

| Code number | Commodity               | Existing EU MRL (mg/kg) | Outcome of the review |
|-------------|-------------------------|-------------------------|-----------------------|
|             | Enzyme definition (existing): triazoxide |                         |                       |
| 500010      | Barley grains           | 0.01*                   | 0.001*                | Recommended(a) |
| 500050      | Oat grains              | 0.01*                   | 0.001*                | Recommended(a) |
| 500070      | Rye grains              | 0.01*                   | 0.001*                | Recommended(a) |
| 500090      | Wheat grains            | 0.01*                   | 0.001*                | Recommended(a) |
| –           | Other commodities of plant and/or animal origin | 0.01*   | –                     | Further consideration needed(b) |

MRL: maximum residue level; CXL: codex maximum residue limit.
*:* Indicates that the MRL is set at the limit of quantification.
(a): MRL is derived from a GAP evaluated at EU level, which is fully supported by data and for which no risk to consumers is identified; no CXL is available (combination G-I in Appendix E).
(b): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A-I in Appendix E).

**References**

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

EFSA (European Food Safety Authority), 2009. Conclusion regarding the peer review of the pesticide risk assessment of the active substance triazoxide. EFSA Journal 2009;7(7):RN-193, 104 pp. https://doi.org/10.2903/j.efsa.2009.193r

EFSA (European Food Safety Authority), 2011. Conclusion on the peer review of the pesticide risk assessment of the active substance triazoxide. EFSA Journal 2011;9(3):2018, 86 pp. https://doi.org/10.2903/j.efsa.2011.2018

EFSA (European Food Safety Authority), 2018a. Completeness check report on the review of the existing MRLs of triazoxide prepared by EFSA in the framework of Article 12 of Regulation (EC) No 396/2005, 9 July 2018. Available online: www.efsa.europa.eu
**Abbreviations**

- a.i.: active ingredient
- a.s.: active substance
- ADI: acceptable daily intake
- AR: additional report
- ARfD: acute reference dose
- BBCH: growth stages of mono- and dicotyledonous plants
- bw: body weight
- CF: conversion factor for enforcement residue definition to risk assessment residue definition
- CXL: codex maximum residue limit
- DAR: draft assessment report
- DAT: days after treatment
- DB: dietary burden
- DM: dry matter
- DT90: period required for 90% dissipation (define method of estimation)
eq residue expressed as a.s. equivalent
EURLs European Union Reference Laboratories for Pesticide Residues (former CRLs)
FAO Food and Agriculture Organization of the United Nations
FS flowable concentrate for seed treatment
GAP Good Agricultural Practice
HPLC-MS/MS high-performance liquid chromatography with tandem mass spectrometry
HR highest residue
IEDI international estimated daily intake
IESTI international estimated short-term intake
ILV independent laboratory validation
InChIKey International Chemical Identifier Key
ISO International Organisation for Standardization
IUPAC International Union of Pure and Applied Chemistry
LOQ limit of quantification
Mo monitoring
MRL maximum residue level
MS Member States
MS mass spectrometry detector
MS/MS tandem mass spectrometry detector
NEDI national estimated daily intake
NESTI national estimated short-term intake
NEU northern European Union
NTMDI national theoretical maximum daily intake
OECD Organisation for Economic Co-operation and Development
PBI plant-back interval
PF processing factor
PHI preharvest interval
PRIMo (EFSA) Pesticide Residues Intake Model
PROFile (EFSA) Pesticide Residues Overview File
QuEChERS Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RA risk assessment
RD residue definition
RMS rapporteur Member State
SANCO Directorate-General for Health and Consumers
SEU southern European Union
SMILES simplified molecular-input line-entry system
STMR supervised trials median residue
TMDI theoretical maximum daily intake
TRR total radioactive residue
**Appendix A – Summary of authorised uses considered for the review of MRLs**

**A.1. Authorised outdoor uses in northern EU**

| Crop and/or situation | MS or country | F or G or I<sup>(a)</sup> | Pests or group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days)<sup>(d)</sup> | Remarks |
|-----------------------|---------------|---------------------------|-----------------------------------|-------------|----------------|-------------------------------|-----------------|---------|
|                        |               |                           |                                   | Type<sup>(b)</sup> | Conc. a.s. | Method | Range of growth stages & season<sup>(c)</sup> | Number min-max | Interval between application (min) | a.s./hl min-max | Water L/ha min-max | Rate and unit |                     |
| Barley DE F            |               | F                          | Seed borne fungal diseases        | FS          | 10 g/L    | Seed treatment | 0 1 n.a. n.a. n.a. | 2 g a.i./100 kg | n.a. Before sowing (max. 1.8 dt seeds/ha) equivalent to max. rate: 3.6 g a.i./ha |
| Oat DE F              |               | F                          | Seed borne fungal diseases        | FS          | 10 g/L    | Seed treatment | 0 1 n.a. n.a. n.a. | 1 g a.i./100 kg | n.a. Before sowing (max. 1.7 dt seeds/ha) equivalent to max. rate: 1.7 g a.i./ha |
| Rye DE F              |               | F                          | Seed borne fungal diseases        | FS          | 10 g/L    | Seed treatment | 0 1 n.a. n.a. n.a. | 1.2 g a.i./100 kg | n.a. Before sowing (max. 1.6 dt seeds/ha) equivalent to max. rate: 1.9 g a.i./ha |
| Wheat DE F            |               | F                          | Seed borne fungal diseases        | FS          | 10 g/L    | Seed treatment | 0 1 n.a. n.a. n.a. | 1.6 g a.i./100 kg | n.a. Before sowing (max. 2.4 dt seeds/ha) equivalent to max. rate: 3.8 g a.i./ha |

FS: flowable concentrate for seed treatment; MRL: maximum residue level; MS: Member State; a.s.: active substance; a.i.: active ingredient; n.a.: not applicable.

<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.

<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 |
|-----------------------------------|-------------|---------|----------------|----------------|----------------|
| Cereals/grass | Barley | Seed treatment: 4.4 g a.s./100 kg seed | Foliage: 10,21, 41 50 grain, straw: 112 | Radiolabel: phenyl-UL-14C-triazoxide (United Kingdom, 2007) |
| | | Seed treatment: 3 and 30 g a.s./100 kg seed | Forage: 42 grain, straw: 180/181 | Radiolabel: phenyl-UL-14C-triazoxide (The United Kingdom, 2011) |

| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) | Comment/source |
|-------------------------------------|-------------|---------|----------------|-----------|----------------|
| Root/tuber crops | Turnip | Seed treatment: 19 g a.s./ha | 131 | Radiolabel: phenyl-UL-14C-triazoxide (EFSA, 2009) |
| Leafy crops | Clover | Seed treatment: 19 g a.s./ha | 131 | Radiolabel: phenyl-UL-14C-triazoxide (EFSA, 2009) |
| Cereal (small grain) | Barley | Seed treatment: 3 and 30 g a.s./100 kg seed | 0 | Primary crop metabolism study used as surrogate for rotational crop study, as pre-emergence treated crop (EFSA, 2009) |

| Processed commodities (hydrolysis study) | Conditions | Stable? | Comment/source |
|------------------------------------------|-------------|---------|----------------|
| Pasteurisation (20 min, 90°C, pH 4) | Not triggered | Residues in grains are not expected to be above 0.001 mg/kg |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | Not triggered | Residues in grains are not expected to be above 0.001 mg/kg |
| Sterilisation (20 min, 120°C, pH 6) | Not triggered | Residues in grains are not expected to be above 0.001 mg/kg |
**Can a general residue definition be proposed for primary crops?**

| Inconclusive | Only cereals (seed treatment) investigated. |
|--------------|------------------------------------------|

**Rotational crop and primary crop metabolism similar?**

| Not applicable | As total residues were below 0.001 mg/kg, identification of individual components in succeeding crops were not undertaken and not required |
|----------------|----------------------------------------------------------------------------------|

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

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

**Plant residue definition for monitoring (RD-Mo)**

Cereals: triazoxide

**Plant residue definition for risk assessment (RD-RA)**

Cereals: sum of triazoxide and metabolites M01 and M02, expressed as triazoxide

**Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs)**

- Matrices with high water content, high oil content, high acid content, dry matrices and straw (EFSA, 2011):
  - HPLC–MS/MS
  - LOQ 0.001 mg/kg, except for straw LOQ 0.005 mg/kg
  - confirmation by monitoring 1 additional transition
  - ILV available
  - QuEChERS for enforcement in routine analysis, LOQ 0.001 mg/kg for high water content and high acid content commodities and LOQ of 0.005 mg/kg for high oil content and dry commodities (EURLs, 2018)

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

| Plant products (available studies) | Category                  | Commodity       | T (°C) | Stability period | Compounds covered | Comment/source       |
|-----------------------------------|---------------------------|-----------------|--------|------------------|-------------------|---------------------|
|                                   | High water content        | Barley forage   | −18    | 24 Months        | Triazoxide        | United Kingdom (2007) |
|                                   | Dry/High starch content   | Barley grain    | −18    | 24 Months        | Triazoxide        | United Kingdom (2007) |
|                                   | Others                    | Barley straw    | −18    | 24 Months        | Triazoxide        | United Kingdom (2007) |

a.s.: active substance; DAT: days after treatment; PBI: plant-back interval; HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation
## B.1.2. Magnitude of residues in plants

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

| 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) |
|----------------------------|------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------|---------------|----------------|-------|
| Barley, oat, rye and wheat grains | NEU              | Mo: < 0.001; < 0.001; < 0.001; < 0.001 RA: –                      | Trials on barley grain compliant with GAP (Germany, 2018). Samples were analysed for parent only; CF 6 is derived from metabolism study. Extrapolation to other cereals is possible | 0.001*                 | Mo: < 0.001   | Mo: < 0.001    | 6     |
| Barley, oat, rye and wheat straw | NEU              | Mo: < 0.001; < 0.001; < 0.001; < 0.001 RA: –                      | Trials on barley straw compliant with GAP (Germany, 2018). Samples were analysed for parent only; CF 6 is derived from metabolism study. Extrapolation to other cereals is possible | 0.005                  | Mo: < 0.001   | Mo: < 0.001    | 6     |

GAP: Good Agricultural Practice; MRL: maximum residue level.
*: Indicates that the MRL is proposed at the limit of quantification.
Mo: residue levels expressed according to the monitoring residue definition.
(a): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, Indoor: indoor EU trials or Country code: if non-EU trials.
(b): Highest residue. The highest residue for monitoring (Mo) refers to the whole commodity and not to the edible portion.
(c): Supervised trials median residue. The median residue for monitoring (Mo) refers to the whole commodity and not to the edible portion.
(d): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment (here based on metabolism studies).
B.1.2.2. Residues in rotational crops

(a) Overall summary

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

|          | Yes | No |
|----------|-----|----|
| Total residues were below 0.001 mg eq./kg in succeeding crops following overdosed trials (9N compared to single application) | 0.001 mg eq./kg |

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

|          | Yes | No |
|----------|-----|----|
| Not triggered | 0.001 mg eq./kg |

B.1.2.3. Processing factors

Not available and not required.

B.2. Residues in livestock

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

| Relevant groups (subgroups) | Dietary burden expressed in mg/kg bw per day | Most critical subgroup | Most critical commodity | Trigger exceeded (Y/N) |
|-----------------------------|---------------------------------------------|------------------------|------------------------|-----------------------|
|                             | Median Maximum                               | Background            | Background            | Y/N                   |
|                             | mg/kg DM Maximum                            | Background            | Background            | Y/N                   |
| Cattle (all)                | 0.002 0.002                                 | 0.05 0.05             | Dairy cattle          | Wheat gluten meal     | No                    |
| Cattle (dairy only)         | 0.002 0.002                                 | 0.05 0.05             | Dairy cattle          | Wheat gluten meal     | No                    |
| Sheep (all)                 | 0.002 0.002                                 | 0.06 0.06             | Lamb                  | Wheat gluten meal     | No                    |
| Sheep (ewe only)            | 0.002 0.002                                 | 0.06 0.06             | Ram/Ewe               | Wheat gluten meal     | No                    |
| Swine (all)                 | 0.001 0.001                                 | 0.04 0.04             | Swine (finishing)     | Barley grain          | No                    |
| Poultry (all)               | 0.003 0.003                                 | 0.05 0.05             | Poultry layer         | Wheat gluten meal     | No                    |
| Poultry (layer only)        | 0.003 0.003                                 | 0.05 0.05             | Poultry layer         | Wheat gluten meal     | No                    |

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

B.2. Nature of residues and methods of analysis in livestock

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

| Livestock (available studies) | Animal          | Dose (mg/kg bw per day) | Duration (days) | Comment/source                                                                 |
|-------------------------------|-----------------|-------------------------|-----------------|-------------------------------------------------------------------------------|
|                               | Lactating ruminants | 0.23                    | 5               | Study performed on lactating goat. Radiolabel: phenyl-UL-14C-triazoxide Dose rate recalculated assuming body weight of 70 kg and feed intake of 2 kg per day (EFSA, 2011) |
### Time needed to reach a plateau concentration in milk and eggs (days)

|          | Milk: 2 days | Eggs: not applicable |
|----------|--------------|---------------------|
| Metabolism in rat and ruminant similar | Not applicable | Not applicable |
| Can a general residue definition be proposed for animals? | Not applicable | Not applicable |
| Animal residue definition for monitoring (RD-Mo) | Not applicable | Not applicable |
| Animal residue definition for risk assessment (RD-RA) | Not applicable | Not applicable |
| Fat soluble residues | Not applicable | – |
| Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs) | Milk, eggs, muscle, fat, liver, kidney: | – |
| | • HPLC–MS/MS | |
| | • For analysis of triazoxide | |
| | • LOQ 0.001 mg/kg | |
| | • ILV available | |
| | • EFSA (2011) | |

bw: body weight; HPLC–MS/MS: high-performance liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

### B.2.1.2. Stability of residues in livestock

Not available and not required.

### B.2.1.3. Magnitude of residues in livestock

Not available and not required.

### B.3. Consumer risk assessment

| ARfD | 0.015 mg/kg bw (EFSA, 2011) |
|------|-----------------------------|
| Highest IESTI, according to EFSA PRIMo (rev.2) | Wheat: 0.6% of ARfD |
| NESTI (% ARfD) | Not assessed in this review |
| Assumptions made for the calculations | The calculation is based on the highest residue levels expected in raw agricultural commodities applying the CF of 6 for risk assessment |

ARfD: acute reference dose; bw: body weight; NESTI: national estimated short-term intake; PRIMo: (EFSA) Pesticide Residues Intake Model; IESTI: international estimated short-term intake.
### B.4. Proposed MRLs

| Code number | Commodity            | Existing EU MRL (mg/kg) | Outcome of the review | Comment |
|-------------|----------------------|-------------------------|-----------------------|---------|
|             |                      |                         | MRL (mg/kg)           |         |
|             |                      |                         | Comment               |         |
| **Enforcement residue definition (existing):** triazoxide | **Enforcement residue definition (proposed):** triazoxide |
| 500010      | Barley grains        | 0.01*                   | 0.001*                | Recommended\(^{(a)}\) |
| 500050      | Oat grains           | 0.01*                   | 0.001*                | Recommended\(^{(a)}\) |
| 500070      | Rye grains           | 0.01*                   | 0.001*                | Recommended\(^{(a)}\) |
| 500090      | Wheat grains         | 0.01*                   | 0.001*                | Recommended\(^{(a)}\) |
| –           | Other commodities of plant and/or animal origin | 0.01* | – | Further consideration needed\(^{(b)}\) |

**MRL:** maximum residue level; **CXL:** codex maximum residue limit.

\(^{(a)}\): MRL is derived from a GAP evaluated at EU level, which is fully supported by data and for which no risk to consumers is identified; no CXL is available (combination G-I in Appendix E).

\(^{(b)}\): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A-I in Appendix E).
Appendix C – Pesticide Residue Intake Model (PRIMo)

• PRIMo(EU)

### Triazoxide

#### Status of the active substance

| Code no. | LOQ (mg/kg bw) | Proposed LOQ |
|----------|---------------|--------------|

#### Toxicological endpoints

| ADI (mg/kg bw per day) | ARfD (mg/kg bw) | Source of ADI | Year of evaluation | Year of evaluation |
|------------------------|-----------------|---------------|--------------------|--------------------|
| 0.0002                 | 0.015           | EFSA          | 2011               | 2015               |

#### No of diets exceeding ADI:

| Commodity/group of commodities | TMDI (range) in % of ADI | 1st contributor to MS diet (in % of ADI) | 2nd contributor to MS diet (in % of ADI) | 3rd contributor to MS diet (in % of ADI) | pTMRLs at LOQ (in % of ADI) |
|--------------------------------|--------------------------|------------------------------------------|------------------------------------------|------------------------------------------|-----------------------------|
| Wheat                         | 16.5                     | 13.3 Rye                                  | 12.0 Oats                                 | 11.6 Rye                                 | 10.5 FRUIT (FRESH OR FROZEN) |
| 26.7 WHO Cluster diet B       | 25.6                     | 23.1 Rye                                  | 21.7 Barley                               | 20.8 Oats                                 | 19.9 FRUIT (FRESH OR FROZEN) |
| 21.6 WHO cluster diet D       | 19.5                     | 17.2 Rye                                  | 15.0 Barley                               | 14.3 Oats                                 | 13.5 FRUIT (FRESH OR FROZEN) |
| 20.0 IT kids/toddler          | 19.9                     | 17.6 Rye                                  | 16.7 Barley                               | 15.8 Oats                                 | 14.8 FRUIT (FRESH OR FROZEN) |
| 15.8 WHO cluster diet E       | 11.8                     | 11.5 Rye                                  | 10.7 Barley                               | 9.8 Oats                                  | 9.0 FRUIT (FRESH OR FROZEN)  |
| 15.4 DE child                 | 12.3                     | 11.7 Rye                                  | 10.7 Barley                               | 9.8 Oats                                  | 9.0 FRUIT (FRESH OR FROZEN)  |
| 15.3 WHO Cluster diet F       | 10.8                     | 10.6 Rye                                  | 9.7 Barley                                | 8.9 Oats                                  | 8.0 FRUIT (FRESH OR FROZEN)  |
| 15.2 NL child                 | 14.2                     | 13.6 Rye                                  | 12.7 Barley                               | 11.8 Oats                                 | 10.9 FRUIT (FRESH OR FROZEN) |
| 13.3 ES child                 | 13.3                     | 12.5 Rye                                  | 11.7 Barley                               | 10.9 Oats                                 | 9.9 FRUIT (FRESH OR FROZEN)  |
| 12.4 IT adult                 | 12.4                     | 11.8 Rye                                  | 11.0 Barley                               | 10.2 Oats                                 | 9.3 FRUIT (FRESH OR FROZEN)  |
| 12.3 PT General population    | 11.8                     | 11.3 Rye                                  | 10.5 Barley                               | 9.7 Oats                                  | 8.9 FRUIT (FRESH OR FROZEN)  |
| 12.0 UK Toddler               | 11.8                     | 11.2 Rye                                  | 10.4 Barley                               | 9.6 Oats                                  | 8.7 FRUIT (FRESH OR FROZEN)  |
| 11.6 IE adult                 | 6.9                      | 6.5 Rye                                   | 6.1 Barley                                | 5.6 Oats                                  | 5.2 FRUIT (FRESH OR FROZEN)  |
| 10.5 SE general population 90th percentile | 9.6 | 9.2 Rye | 8.8 Barley | 8.3 Oats | 7.9 FRUIT (FRESH OR FROZEN) |

### Conclusion:

The estimated Theoretical Maximum Daily Intakes (TMDI), based on pTMRLs were below the ADI. A long-term intake of residues of Triazoxide is unlikely to present a public health concern.
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 leads to an exposure equivalent to 100% of the ARfD.

| Highest % of ARfD/ADI Commodity | pTMRL/MRL (mg/kg) |
|---------------------------------|------------------|
| Wheat                           | 0.006/-          |
| Rye                             | 0.006/-          |
| Oats                            | 0.006/-          |
| Barley                          | 0.006/-          |

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

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

Conclusion:

For Triazoxide, 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.
Appendix D – Input values for the exposure calculations

### D.1. Livestock dietary burden calculations

| Feed commodity          | Median dietary burden | Maximum dietary burden |
|-------------------------|-----------------------|------------------------|
|                         | Input value (mg/kg)   | Comment                | Input value (mg/kg) | Comment                |
| Risk assessment residue definition: sum of triazoxide and metabolites M01 and M02, expressed as triazoxide compound |
| Barley, grain           | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Brewer's grain, dried(a) | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Oat, grain              | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Rye, grain              | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Triticale, grain        | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Wheat, grain            | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Wheat, distiller's grain (dry)(a) | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Wheat gluten, meal(a)   | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Wheat, milled by-pdts(a) | 0.006                 | STMRMo × CF (6)        | 0.006               | STMRMo × CF (6)        |
| Barley, straw           | 0.006                 | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Oat, straw              | 0.006                 | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Rye, straw              | 0.006                 | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Triticale, straw        | 0.006                 | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Wheat, straw            | 0.006                 | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |

STMR: supervised trials median residue; HR: highest residue; CF: conversion factor; Mo: monitoring.
(a): For by-products, no default processing factor was applied because triazoxide is applied early in the growing season and residues are expected to be below the LOQ of 0.001 mg/kg. Concentration of residues in these commodities is therefore not expected.

### D.2. Consumer risk assessment

| Commodity          | Chronic risk assessment | Acute risk assessment |
|--------------------|-------------------------|-----------------------|
|                    | Input value (mg/kg)     | Comment                | Input value (mg/kg) | Comment                |
| Risk assessment residue definition: sum of triazoxide and metabolites M01 and M02, expressed as triazoxide compound |
| Wheat grain        | 0.006                   | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Rye grain          | 0.006                   | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Oats grain         | 0.006                   | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |
| Barley grain       | 0.006                   | STMRMo × CF (6)        | 0.006               | HRMo × CF (6)          |

STMR: supervised trials median residue; HR: highest residue; CF: conversion factor; Mo: monitoring.
Appendix E – Decision tree for deriving MRL recommendations

Evaluation of the GAPs and available residues data at EU level

- GAP or DB ≥ 0.1 mg/kg AN in EU?
  - Yes
    - MRL derived in Section 3?
      - Yes
        - MRL fully supported by data?
          - Yes
          - MRL is recommended.
        - No
      - No
  - No

Consumer risk assessment for GAPs evaluated at EU level – EU scenarios

- Not considered for the RA.
- Current EU MRL is included in the RA?
  - Yes
    - Risk identified?
      - Yes
        - Fall-back MRL available?
          - Yes
          - MRL is recommended.
        - No
      - No
  - No
- Tentative median/highest values are included in the RA.
  - Yes
    - Risk identified?
      - Yes
        - Fall-back MRL available?
          - Yes
          - MRL is recommended.
        - No
      - No
  - No

Recommendations resulting from EU authorisations and import tolerances

- (A) Specific LOQ or default MRL?
  - Yes
  - (B) Specific LOQ or default MRL?
    - Yes
      - (C) Maintain current EU MRL?
        - Yes
        - (D) Establish tentative EU MRL?
          - Yes
          - (E) Specific LOQ or default MRL?
            - Yes
            - (F) MRL is recommended.
          - No
        - No
      - No
    - No
  - No
- (D) Establish tentative EU MRL?
  - Yes
    - Specific LOQ or default MRL?
      - Yes
      - Fall-back MRL available?
        - Yes
        - MRL is recommended.
        - No
      - No
    - No
- (F) Specific LOQ or default MRL?
  - Yes
    - MRL is recommended.
  - No

Comparison with CXLs
Comparison of the EU recommendation with the existing CXL

- **(I)** Maintain EU recommendation indicating that no CXL is available.
- **(II)** Maintain EU recommendation indicating CXL is not compatible.
- **(III)** Maintain EU recommendation indicating that CXL is covered.
- **(IV)** Maintain EU recommendation; higher CXL is not safe for consumer.
- **(V)** Maintain current CXL or EU recommendation?
- **(VI)** Maintain EU recommendation; higher CXL is not safe for consumer.
- **(VII)** CXL is recommended; EU recommendation is covered as well.

Consumer risk assessment with consideration of the existing CXL

- Input values for the RA remain unchanged.
- Input values for the RA remain unchanged.
- Input values for the RA remain unchanged.
- CXL is included in the RA.
- CXL is supported by data?
- Codex median/highest residues are included in the RA.
- Risk identified?

Recommendations with consideration of the existing CXL

- **(I)** Maintain EU recommendation indicating that no CXL is available.
- **(II)** Maintain EU recommendation indicating CXL is not compatible.
- **(III)** Maintain EU recommendation indicating that CXL is covered.
- **(IV)** Maintain EU recommendation; higher CXL is not safe for consumer.
- **(V)** Maintain current CXL or EU recommendation?
- **(VI)** Maintain EU recommendation; higher CXL is not safe for consumer.
- **(VII)** CXL is recommended; EU recommendation is covered as well.
### Appendix F – Used compound codes

| Code/trivial name     | Chemical name/SMILES notation/InChiKey<sup>a</sup> | Structural formula<sup>b</sup> |
|-----------------------|---------------------------------------------------|-------------------------------|
| triazoxide            | 7-chloro-3-imidazol-1-yl-1,2,4-benzotriazine 1-oxide  
Clc1ccc2nc(n[n+]([O-])c2c1)n1ccnc1  
IQGKIPDJXCAMSM-UHFFFAOYSA-N | ![Structural formula](image1.png) |
| M01 desoxy-triazoxide | 7-chloro-3-(1H-imidazol-1-yl)-1,2,4-benzotriazine  
Clc1ccc2nc(nnc2c1)n1ccnc1  
DGTGEGYFJGFHNA-UHFFFAOYSA-N | ![Structural formula](image2.png) |
| M02 triazoxide-amino  | 7-chloro-1-oxo-1,5,2,4-benzotriazin-3-amine  
[O-][n+]1nc(N)nc2ccc(Cl)cc21  
OXI0AZXVNKSG-UHFFFAOYSA-N | ![Structural formula](image3.png) |

SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.  
<sup>a</sup>: ACD/Name 2017.2.1 ACD/Labs 2017.2.1 Release (File version N40E41, Build 96719, 6 September 2017).  
<sup>b</sup>: ACD/ChemSketch 2017.2.1 ACD/Labs 2017.2.1 Release (File version C40H41, Build 99535, 14 February 2018).