Review of the existing maximum residue levels for fenbutatin oxide 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 fenbutatin oxide. Although this active substance is no longer authorised within the EU due to the lack of toxicological data on di-hydroxy fenbutatin oxide, a compound observed in the metabolism studies but also present as an impurity in the technical active substance, MRLs established by the Codex Alimentarius Commission (CXLs) are still in place. Lacking a full toxicological characterisation of this compound, it was not possible for EFSA to perform an assessment of these CXLs and their incorporation in European legislation cannot be recommended. Nevertheless, available data allowed EFSA to propose a marker residue and a limit of quantification (LOQ) for enforcement against potential illegal uses.

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**Summary**

Fenbutatin oxide was initially not included in Annex I to Directive 91/414/EEC by Commission Decision 2008/934/EC. Following a resubmission application, fenbutatin oxide was subsequently approved by Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 as a active substance, in accordance with the provision of Regulation (EC) No 1107/2009. As fenbutatin oxide 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. To collect the relevant pesticide residues data, EFSA asked Belgium, the designated rapporteur Member State (RMS), to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report.

Meanwhile, the approval of fenbutatin oxide was withdrawn by means of Commission Implementing Regulation (EU) No 486/2014 of 12 May 2014. In order to verify whether import tolerances may still be in place in some Member States and to collect additional information on the available analytical methods for enforcement against illegal uses, a request for additional information was addressed to the Member States and the EURLs in the framework of a completeness check period which was initiated by EFSA on 28 July 2017 and finalised on 28 September 2017. No further information was provided by Member States, while the EURLs adequately reported additional information on the availability of analytical methods for enforcement in routine analyses. After having considered all the information provided, EFSA prepared a completeness check report which was made available to Member States on 11 October 2017.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC, the MRLs established by the Codex Alimentarius Commission and the additional information provided by the RMS and the EURLs, EFSA prepared in October 2017 a draft reasoned opinion, which was circulated to Member States for consultation via a written procedure. Comments received by 24 November 2017 were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

Although the use of fenbutatin oxide is no longer authorised within the European Union (EU) and uses authorised in third countries were not reported to EFSA, the Codex Limits (CXLs) for fenbutatin oxide which were previously evaluated by the JMPR are currently still in place. Nevertheless, due to the lack of toxicological data for the compound di-hydroxy fenbutatin oxide observed in the metabolism studies and in the technical active substance, it was not possible for EFSA to perform an assessment of the CXLs. Consequently, incorporation of these CXLs in the European legislation is not recommended, including those that are currently still in place at EU level.

In order to assist risk managers in applying the most appropriate enforcement measures (against potential illegal uses), EFSA assessed the available data with particular attention to the analytical methods and the nature of residues in plants and livestock.

Primary crop metabolism of fenbutatin oxide was investigated in apple, celery and radish following foliar application, while rotational crop metabolism was investigated in wheat, lettuce, turnips and radishes. Based on the available data, and given the relevance of unchanged parent compound after foliar and bare soil treatments, parent compound is considered to be the most adequate marker for enforcement against the potential illegal use of fenbutatin oxide in plants. It is expected that enforcement laboratories will be able to enforce this compound with a limit of quantification (LOQ) of 0.01 mg/kg in all plant commodities, except in complex matrices (e.g. tea, herbal infusions, cocoa, hops and spices). For these plant commodities, in the absence of fully validated analytical method, a higher LOQ of 0.05 is tentatively proposed.

Livestock metabolism of fenbutatin oxide was investigated in a lactating goat and in laying hens. Since the metabolism in rats and ruminants was found to be similar, the main findings of the ruminants study can be extrapolated to pigs. Also in this case, the parent compound is considered to be a valid marker for enforcement against the potential illegal use of fenbutatin oxide in animals. It is expected that enforcement laboratories will be able to enforce these compounds with a LOQ of 0.02 mg/kg in all animal commodities. As the log $P_{ow}$ for fenbutatin oxide is higher than 3 (5.15) and considering that in the ruminants study findings in fat were found to be higher than in muscle, this residue is to be considered fat soluble.

Considering that the enforcement against potential illegal uses falls under the remit of risk managers, EFSA is not in a position to recommend whether the default MRL of 0.01 mg/kg, as defined by Regulation (EC) No 396/2005, or whether the setting of specific LOQ values for plant and animal commodities should apply. It is noted, however, that for fenbutatin oxide, LOQ values of 0.05 mg/kg in complex matrices of plant origin, 0.01 mg/kg in all other plant commodities and 0.02 mg/kg in animal commodities, would provide a satisfactory level of protection for the European consumers.
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Review of the existing MRLs for fenbutatin oxide

Background

Regulation (EC) No 396/2005¹ (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/EEC² a reasoned opinion on the review of the existing MRLs for that active substance. Fenbutatin oxide was evaluated in the framework of Directive 91/414/EEC with Belgium designated as the rapporteur Member State (RMS). In 2008, a decision on the non-inclusion of the active substance was taken by Commission Decision 2008/934/EC³ following the voluntary withdrawal of the support for the active substance by the applicant. The applicant submitted a new application requesting the accelerated procedure regarding the inclusion of the active substance in Annex I of Directive 91/414/EEC. Based on the EFSA conclusion which was issued on 1 September 2010 (EFSA, 2010), the decision to approve the active substance fenbutatin oxide in accordance with the provision of Regulation (EC) 1107/2009⁴, repealing the provisions of Directive 91/414/EEC, was taken. As fenbutatin oxide was included in Annex I to Council Directive 91/414/EEC on 7 March 2011 by means of Commission Directive 2011/30/EU⁵ and has been deemed to be approved under Regulation (EC) No 1107/2009 in accordance with Commission Implementing Regulation (EU) No 540/2011⁶, EFSA initiated the review of all existing MRLs for that active substance.

According to the legal provisions, EFSA shall base its reasoned opinion in particular on the relevant assessment report prepared under Directive 91/414/EEC. It should be noted, however, that, in the framework of Directive 91/414/EEC, only a few representative uses are evaluated, whereas MRLs set out in Regulation (EC) No 396/2005 should accommodate all uses authorised within the European Union (EU), and uses authorised in third countries that have a significant impact on international trade. The information included in the assessment report prepared under Directive 91/414/EEC is therefore insufficient for the assessment of all existing MRLs for a given active substance.

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.

Belgium, the designated RMS in the framework of Directive 91/414/EEC, was asked to complete the PROFile for fenbutatin oxide and to prepare a supporting evaluation report. The evaluation report was submitted to EFSA on 18 July 2012 and made available to the Member States. A PROFile was not considered relevant since no Good Agricultural Practices (GAPs) were notified to the RMS at the time of the preparation of the evaluation report.

In order to verify whether import tolerances may still be in place in some Member States and to collect additional information on the available analytical methods for enforcement against illegal uses, a request for additional information was still addressed to the Member States and the EURLs in the framework of a completeness check period which was initiated by EFSA on 28 July 2017 and finalised on 28 September 2017. No further information was provided by Member States while the EURLs

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¹ Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.
² Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32. Repealed by Regulation (EC) No 1107/2009.
³ Commission Decision 2008/934/EC of 5 December 2008 concerning the non-inclusion of certain active substances in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing these substances (notified under document number C(2008) 7637) OJ L 333, 11.12.2008, p. 11–14.
⁴ Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.
⁵ Commission Directive 2011/30/EU of 7 March 2011 amending Council Directive 91/414/EEC to include fenbutatin oxide as active substance and amending Commission Decision 2008/934/EC. OJ L 61, 8.3.2011, p. 14–17.
⁶ Commission Implementing Regulation (EU) No 540/2011 of 25 May 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p.1–186.
adequately reported additional information on the availability of analytical methods for enforcement in routine analyses. EFSA prepared a completeness check report which was made available to all Member States on 11 October 2017 and no further clarifications were sought from Member States.

Based on the conclusions derived by EFSA in the framework of Directive 91/414/EEC and the MRLs established by the Codex Alimentarius Commission, EFSA prepared in October 2017 a draft reasoned opinion, which was submitted to Member States for commenting via a written procedure. All comments received by 24 November 2017 were considered by EFSA during the finalisation of the reasoned opinion.

In addition, key supporting documents to this reasoned opinion are the evaluation report provided by the EURoPs (2017), the completeness check report (EFSA, 2017a), and the Member States consultation report (EFSA, 2017b). These reports are developed to address all issues raised in the course of the review, from the initial completeness check to the reasoned opinion.

Considering the importance of the completeness check and consultation report, all documents are considered as background documents to this reasoned opinion and, thus, are made publicly available. Furthermore, a screenshot of the Report sheet of the PRIMo(EU) is presented in Appendix A.

**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**

Fenbutatin oxide is the ISO common name for bis[tris(2-methyl-2-phenylpropyl)tin]oxide (IUPAC). Fenbutatin oxide belongs to the group of non-systemic organostannic compounds which are used as acaricides with contact and stomach action. Fenbutatin oxide is used to control all motile stages of a wide range of phytophagous mites. It works by inhibition of a variety of biochemical processes. The chemical structure of the active substance and its main metabolite are reported in Appendix B.

Fenbutatin oxide was evaluated in the framework of Directive 91/414/EEC with Belgium as the designated RMS. The representative uses supported for the peer review process was as glasshouse insecticide on tomato for the control of mites. Following the draft assessment report (DAR) submission, however, the applicant voluntarily withdrew, in accordance with Article 11(e) of Regulation (EC) No 1490/2002, its support for the inclusion of fenbutatin oxide in Annex I to Directive 91/414/EEC. Consequently, a first decision on non-inclusion of this active substance was published by means of Commission Decision 2008/934/EC. In accordance with the provision laid down in Article 13 of Regulation (EC) No 33/2008, a resubmission application for this active substance was subsequently made for the same representative uses. Following the peer review, which was carried out by EFSA (2010), a decision on inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Directive 2011/30/EU, which entered into force on 1 June 2011. According to Regulation (EU) No 540/2011, fenbutatin oxide was deemed to have been approved under Regulation (EC) No 1107/2009, with the condition that the applicant, at whose request fenbutatin oxide has been approved, provides further confirmatory information on genotoxicological potential, ecotoxicological relevance, spectra, storage stability and methods of analysis in the formulation for the impurity di-hydroxy fenbutatin oxide (SD 31723). The approval was restricted to uses as acaricide in greenhouses only. The applicant, however, did not submit any confirmatory information; consequently, the approval was withdrawn by Commission Implementing Regulation (EU) No 486/2014 of 12 May 2014.

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7 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.
8 Commission Regulation (EC) No 33/2008 of 17 January 2008 laying down detailed rules for the application of Council Directive 91/414/EEC as regards a regular and an accelerated procedure for the assessment of active substances which were part of the programme of work referred to in Article 8(2) of that Directive but have not been included into its Annex I. OJ L 15, 18.1.2008, p. 5–12.
9 Commission Regulation (EU) No 488/2014 of 12 May 2014 amending Regulation (EC) No 1881/2006 as regards maximum levels of cadmium in foodstuffs. OJ L 138, 13.5.2014, p. 75–79.
The EU MRLs for fenbutatin oxide are set in Annexes II and IIIIB of Regulation 396/2005/EC and the Codex maximum residue limits (CXLs) for fenbutatin oxide were also established by the Codex Alimentarius Commission (CAC).

According to the expiry of the approval under Regulation (EC) No 1107/2009, plant protection products containing fenbutatin oxide are no longer authorised in EU Member States (authorisations for emergency situations in plant protection granted in application of Article 53 of Regulation (EC) No 1107/2009 are not considered in the context of this reasoned opinion). For the purpose of this MRL review, Member States did not report any use authorised in third countries that might have a significant impact on international trade.

**Assessment**

Although the use of fenbutatin oxide is no longer authorised within the EU and uses authorised in third countries were not reported to EFSA, the CXLs for fenbutatin oxide were previously evaluated by the JMPR (FAO, 1993) and they are currently still in place. Exposure of European consumers to residues of this active substance (resulting from the use of fenbutatin oxide outside the EU) can therefore not be excluded and a detailed assessment of these CXLs is in principle required.

It is noted however that a lack of toxicological data for the compound di-hydroxy fenbutatin oxide (SD 31723) found in the metabolism studies but also present as an impurity in the technical active substance, was previously identified by EFSA (2010), which finally resulted in the non-approval of the active substance at EU level. Since these uncertainties apply to the active substance in general, incorporation of these CXLs in European legislation is not recommended, including those that are currently still in place at EU level.

However, risk managers might need to enforce against the potential illegal use of fenbutatin oxide within the EU, and against the presence of illegitimate residue levels in imported products. In order to assist risk managers in applying the most appropriate enforcement measures, EFSA assessed the available data with particular attention to the analytical methods and the nature of residues in plants and livestock. EFSA mainly bases its assessment on the draft assessment report (DAR), the additional report (AR) and their addenda prepared under Council Directive 91/414/EEC (Belgium, 2006, 2009, 2010), the conclusion on the peer review of the pesticide risk assessment of the active substance fenbutatin oxide (EFSA, 2010), the evaluation report prepared by the RMS in the framework of this review (Belgium, 2012) and the evaluation report submitted by the EURLs during the completeness check (EURLs, 2017).

1. **Residues in plants**

Primary crop metabolism of fenbutatin oxide was investigated in apple (fruit crop), celery (leafy vegetable) and radish (root and tuber vegetable) following foliar application using radiolabelled fenbutatin oxide. Rotational crop metabolism of fenbutatin oxide was investigated in radishes, wheat, turnips and lettuce planted after bare soil application of radiolabelled fenbutatin oxide (Belgium, 2006, 2009).

In both primary and rotational crops, a major proportion of the total residue was present as parent fenbutatin oxide accounting for up to 96% in celery samples (leaves and stems). In apples, the contributions to the total radioactive residue (TRR) of the different compounds identified were not reported but the absolute amounts detailed in the study for the identified compounds, indicated that the parent was the major component of the residue in the fruit (0.78 mg eq./kg). In this study, an additional compound, not observed in the studies on celery and radish, was also identified: di-hydroxy fenbutatin oxide (SD 31723), reaching a maximum of 0.025 mg eq./kg, 121 days after the first treatment. This metabolite was also found in immature lettuce (up to 2.6% TRR), radish tops (up to 5.8% TRR) and radish roots (up to 3.6% TRR) from the confined rotational crop studies. According to the whole data evaluated during the peer review, there are indications that this compound could represent an impurity of the technical active substance; however, it could not be concluded whether its presence results from the metabolism/degradation of the parent compound or if it has to be considered as an impurity (EFSA, 2010).

During the peer review, several gas chromatography with mass spectrometry (GC-MS) methods have been reported for the determination of fenbutatin oxide in matrices with high water (tomatoes, apple) and high acid (citrus) content (limit of quantification (LOQ) of 0.05 mg/kg) (Belgium, 2009). All of these methods consist of a derivatisation of fenbutatin oxide prior to chromatographic analysis but
the efficiency of the derivatisation step was not sufficiently validated. Therefore, during the peer review, methods were considered not acceptable and a data gap was identified (EFSA, 2010). During the completeness check, information on the availability of analytical methods for the enforcement of fenbutatin oxide was received by the EURLs (2017). On the basis of the information provided, it is concluded that during routine analyses, laboratories should be able to enforce fenbutatin oxide in plant commodities (high water, high acid, high fat content and dry matrices) at the LOQ of 0.01 mg/kg by applying the acidified Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) method. Fully validated analytical methods are not available for the enforcement in complex matrices (e.g. tea, herbal infusions, cocoa, hops and spices). For these plant commodities, in absence of fully validated analytical method, a higher LOQ of 0.05 is indicatively proposed.

Hence, based on the available data, and given the relevance of unchanged parent compound after foliar and soil treatment, fenbutatin oxide is considered to be the most adequate marker for enforcement against the potential illegal use of fenbutatin oxide in plants, and it is expected that enforcement laboratories will be able to enforce this compound at least in the main four matrices.

2. Residues in livestock

Livestock metabolism of fenbutatin oxide was investigated in the framework of Directive 91/414/EEC (Belgium, 2006, 2009).

In a lactating goat receiving 80 mg/kg body weight (bw) per day radiolabelled fenbutatin oxide for 7 consecutive days, the major part of the total radioactivity administered (77%) was excreted via faeces as unchanged parent compound.

The highest residue levels were observed in liver and kidney (0.40 and 0.28 mg eq./kg, respectively). Fat matrices were also characterised by non-negligible residue levels (0.035-0.16 mg eq./kg) confirming the liposolubility of the parent compound. Residues in muscle accounted for 0.097 mg eq./kg. In milk, residue levels were below the LOQ of the analytical method used in the study (0.04 mg/kg).

Fenbutatin oxide and its di-hydroxy metabolite (SD 31723) were the only compounds recovered in liver and kidney while only the parent compound was identified in both muscle and fat. Nevertheless, detailed information on their absolute amounts and their contributions to the TRR was not reported in the study.

Therefore, the main route of degradation of fenbutatin oxide in lactating goats can be described mainly as a di-hydroxylation of the parent compound to generate the di-hydroxy fenbutatin oxide. Since the metabolism in rats and ruminants was found to be similar, the main findings of this study can be extrapolated to pigs.

In the poultry study, laying hens received for 7 consecutive days, 1.76 mg fenbutatin oxide per day, corresponding to 14 mg/kg fenbutatin oxide in the total dietary ration.

As observed in goat, the major part of the radioactivity administered to hens was excreted as unchanged fenbutatin oxide (93.3% of the total administered dose).

The highest residue levels were observed in liver and kidney (0.027 and 0.015 mg eq./kg, respectively) whereas the total radioactive residues in fat and muscle were below the limit of detection of the analytical method (0.002 mg/kg).

Attempts were made to fractionate and characterise the chemical nature of the total residues in the liver. More than 50% of the TRR could be recovered from the liver matrix in the organo-soluble phase after protease digestion and exhaustive solvent extraction. Thin-layer chromatography (TLC) analysis by co-chromatography of the organo-soluble extract showed the presence of two metabolites that were tentatively characterised as the unchanged parent compound and the metabolite di-hydroxy fenbutatin oxide. These compounds did not occur at a level greater than 0.01 mg/kg.

No further characterisation of the radioactivity was performed in kidney and muscle/fat due to the low levels of radioactive residues recovered in those matrices (0.015 mg/kg and < 0.002 mg/kg, respectively).

The TRRs in eggs ranged from < 0.002 mg/kg to 0.015 mg/kg. Following attempts to fractionate and characterise the chemical nature of the highest residue, parent compound was found to represent indicatively 40–50% of the TRR.

Livestock feeding studies on lactating goats and hens were also evaluated during the peer review (Belgium, 2006, 2009). In these studies, after administration of fenbutatin oxide at different dose levels, animal tissues, milk and eggs were analysed for fenbutatin oxide, di-hydroxy fenbutatin oxide and an additional metabolite (SD 33608). Findings from these studies support the residue behaviour observed in the metabolism studies.
In cows dosed with fenbutatin oxide at 11 and 96 mg/kg in the total diet for consecutive 22 days, the highest residue levels were found in liver (0.05 and 0.11 mg/kg for parent and di-hydroxy fenbutatin oxide, respectively), kidney (0.15 and 0.03 mg/kg for parent and di-hydroxy fenbutatin oxide, respectively), fat (0.05 and < 0.02 mg/kg for parent and di-hydroxy fenbutatin oxide, respectively) and milk cream (0.08 mg/kg for the parent) from the highest dose group. Metabolite SD 33608 was always below the LOQ of 0.02 mg/kg.

In hens dosed with fenbutatin oxide at 5 and 25 mg/kg for 28 consecutive days, the highest residue levels were found in kidney (0.03 mg/kg for both parent and di-hydroxy fenbutatin oxide), in liver (up to 0.04, 0.12 and 0.04 mg/kg for parent, di-hydroxy fenbutatin oxide and SD 33608, respectively) and in eggs yolk (0.25 mg/kg for the parent) from the highest dose group.

During the peer review, an analytical method for the enforcement of fenbutatin oxide in animal tissues and in milk by using high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) was evaluated and considered sufficiently validated at the LOQ of 0.02 mg/kg. This method was validated for cow meat, cow milk, bovine fat and bovine liver. Independent laboratory validation was also provided and considered acceptable (Belgium, 2009; EFSA, 2010). Although an analytical method for the enforcement in eggs is not available, considering that the reported method has been successfully validated in all other animal matrices, EFSA assumes that the LOQ of 0.02 mg/kg would be achievable in eggs as well. No validation data for fenbutatin oxide residues in commodities of animal origin is available to the EURLs (EURLs, 2017).

Hence, on the basis of the available studies, parent compound only is considered to be a valid marker for enforcement against the potential illegal use of fenbutatin oxide in livestock and it is expected that enforcement laboratories will be able to enforce this compound in animal commodities. As the log P_{ow} for fenbutatin oxide is higher than 3 (5.15) and considering that in the ruminants study findings in fat were found to be higher than in muscle, this residue is considered fat soluble.

### 3. Consumer risk assessment

The toxicological assessment of fenbutatin oxide was peer reviewed under Directive 91/414/EEC, which resulted in an acceptable daily intake (ADI) and an acute reference dose (ARfD) being established at 0.05 mg/kg bw per and 0.1 mg/kg bw, respectively (EFSA, 2010). It is noted however that a lack of full toxicological data package for the compound di-hydroxy fenbutatin oxide (SD 31723) was previously identified by EFSA (2010), which finally resulted in the non-approval of the active substance at EU level. Moreover, the available mammalian toxicity data indicate that this compound has a higher toxicity than fenbutatin oxide. Toxicological reference values derived for fenbutatin oxide are therefore to be considered with caution and, since these uncertainties apply to the active substance in general, an accurate assessment of the CXLs that are currently in place is not possible.

Nevertheless, in order to assess whether the reported LOQ values are sufficiently protective for European consumers, chronic intake calculations were performed using revision 2 of the EFSA PRIMO (EFSA, 2007). These calculations were carried out assuming residues present at the LOQs of 0.05 mg/kg in complex matrices of plant origin, 0.01 mg/kg in all other plant commodities and 0.02 mg/kg in all commodities of animal origin.

The calculated exposures were compared with the toxicological reference value for fenbutatin oxide. The highest chronic exposure was calculated for French toddlers, representing 2% of the ADI, and the highest acute exposure was calculated for milk and milk products, representing 2.5% of the ARfD. EFSA highlights that this calculation does not reflect real exposure of consumers to fenbutatin oxide residues. This theoretical calculation only indicates that the above-reported LOQ values would provide a satisfactory level of protection for the European consumers.

### Conclusions and recommendations

Although the use of fenbutatin oxide is no longer authorised within the EU and uses authorised in third countries were not reported to EFSA, the CXLs for fenbutatin oxide which were previously evaluated by the JMPR are currently still in place. Nevertheless, due to the lack of toxicological data for the compound di-hydroxy fenbutatin oxide observed in the metabolism studies and in the technical active substance, it was not possible for EFSA to perform an assessment of the CXLs. Consequently, incorporation of these CXLs in the European legislation is not recommended, including those that are currently still in place at EU level.
In order to assist risk managers in applying the most appropriate enforcement measures (against potential illegal uses), EFSA assessed the available data with particular attention to the analytical methods and the nature of residues in plants and livestock.

Primary crop metabolism of fenbutatin oxide was investigated in apple, celery and radish following foliar application, while rotational crop metabolism was investigated in wheat, lettuce, turnips and radishes. Based on the available data, and given the relevance of unchanged parent compound after foliar and bare soil treatments, parent compound is considered to be the most adequate marker for enforcement against the potential illegal use of fenbutatin oxide in plants. It is expected that enforcement laboratories will be able to enforce this compound with a LOQ of 0.01 mg/kg in all plant commodities, except in complex matrices (e.g. tea, herbal infusions, cocoa, hops and spices). For these plant commodities, in the absence of fully validated analytical method, a higher LOQ of 0.05 is tentatively proposed.

Livestock metabolism of fenbutatin oxide was investigated in a lactating goat and in laying hens. Since the metabolism in rats and ruminants was found to be similar, the main findings of the ruminants study can be extrapolated to pigs. Also in this case, the parent compound is considered to be a valid marker for enforcement against the potential illegal use of fenbutatin oxide. It is expected that enforcement laboratories will be able to enforce these compounds with a LOQ of 0.02 mg/kg in all animal commodities. As the log $P_{ow}$ for fenbutatin oxide is higher than 3 (5.15) and considering that in the ruminants study findings in fat were found to be higher than in muscle, this residue is to be considered fat soluble.

Considering that the enforcement against potential illegal uses falls under the remit of risk managers, EFSA is not in a position to recommend whether the default MRL of 0.01 mg/kg, as defined by Regulation (EC) No 396/2005, or whether the setting of specific LOQ values for plant and animal commodities should apply. It is noted however that for fenbutatin oxide, LOQ values of 0.05 mg/kg in complex matrices of plant origin, 0.01 mg/kg in all other plant commodities and 0.02 mg/kg in animal commodities, would provide a satisfactory level of protection for the European consumers.

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Abbreviations

a.s. active substance
ADI acceptable daily intake
AR additional report
ARfD acute reference dose
bw body weight
CAC Codex Alimentarius Commission
CXL codex maximum residue limit
DAR draft assessment report
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
GAP Good Agricultural Practice
GC-MS gas chromatography with mass spectrometry
ISO International Organisation for Standardization
IUPAC International Union of Pure and Applied Chemistry
JMPR Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LOQ limit of quantification
MRL maximum residue level
OECD Organisation for Economic Co-operation and Development
P_{ow} partition coefficient between n-octanol and water
PRIMo (EFSA) Pesticide Residues Intake Model
PROFile (EFSA) Pesticide Residues Overview File
QuEChERS Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RMS rapporteur Member State
SMILES simplified molecular-input line-entry system
TLC thin-layer chromatography
TRR total radioactive residue
WHO World Health Organization
Appendix A – Pesticide Residue Intake Model (PRImo)

**PRImo(EU)**

### Fenbutatin oxide

| Toxicological end points | ADI (mg/kg bw) | ARfD (mg/kg bw) | Source of ADI | Year of evaluation |
|--------------------------|----------------|-----------------|---------------|-------------------|
| LOQ (mg/kg bw)           | 0.05           | 0.1             | EFSA          | 2010              |

### Chronic risk assessment

| Commodity/ group of commodities | TMDI (range) in % of ADI | No of diets exceeding ADI: |
|---------------------------------|--------------------------|-----------------------------|
|                                 | minimum – maximum        | 0 - 3                       |

#### Highest calculated TMDI values in % of ADI

| Diet                     | MS Diet | Commodity/ group of commodities | TMDI (range) in % of ADI | 2nd contributor to MS diet | 3rd contributor to MS diet | pTMRLs at LOQ (in % of ADI) |
|--------------------------|---------|---------------------------------|--------------------------|----------------------------|----------------------------|-----------------------------|
| FR toddler               | 1.7     | PRODUCTS OF ANIMAL ORIGIN       | 0.3 VEGETABLES            | 0.2 FRUIT (FRESH OR FROZEN)| 0.1 VEGETABLES             |                             |
| UK infant                | 1.7     | PRODUCTS OF ANIMAL ORIGIN       | 0.2 SUGAR PLANTS          | 0.1 VEGETABLES             | 0.1 VEGETABLES             |                             |
| NL child                 | 1.3     | PRODUCTS OF ANIMAL ORIGIN       | 0.2 FRUIT (FRESH OR FROZEN) | 0.1 VEGETABLES            | 0.1 VEGETABLES            |                             |
| FR infant                | 1.1     | PRODUCTS OF ANIMAL ORIGIN       | 0.2 VEGETABLES            | 0.1 FRUIT (FRESH OR FROZEN) | 0.1 VEGETABLES            |                             |
| UK Toddler               | 0.9     | PRODUCTS OF ANIMAL ORIGIN       | 0.1 CEREALS               | 0.1 VEGETABLES             | 0.1 VEGETABLES             |                             |
| DE child                 | 0.9     | PRODUCTS OF ANIMAL ORIGIN       | 0.1 CEREALS               | 0.1 VEGETABLES             | 0.1 VEGETABLES             |                             |
| DK child                 | 0.7     | PRODUCTS OF ANIMAL ORIGIN       | 0.1 CEREALS               | 0.1 VEGETABLES             | 0.1 VEGETABLES             |                             |
| SE general population 90th percentile | 0.7 | PRODUCTS OF ANIMAL ORIGIN | 0.1 CEREALS | 0.1 VEGETABLES | 0.1 VEGETABLES |                             |

**Conclusion:**

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

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### Review of the existing MRLs for fenbutatin oxide

#### Acute risk assessment/children

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) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) |
|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|
| 2.5 Milk and milk products:      | 0.00/-                      | 2.5 Milk and milk                 | 0.01/-                      | 0.5 Pumpkins                      | 0.05/-                      | 0.5 Pumpkins                      | 0.01/-                      |
| 1.5 Potatoes                     | 0.01/-                      | 1.5 Melons                        | 0.01/-                      | 0.4 Watermelons                   | 0.01/-                      | 0.4 Watermelons                   | 0.01/-                      |
| 1.5 Melons                       | 0.01/-                      | 1.2 Watermelons                   | 0.01/-                      | 0.4 Melons                        | 0.01/-                      | 0.4 Melons                        | 0.01/-                      |
| 1.3 Oranges                      | 0.01/-                      | 1.1 Potatoes                      | 0.01/-                      | 0.4 Chinese cabbage               | 0.01/-                      | 0.4 Chinese cabbage               | 0.01/-                      |
| 1.2 Watermelons                  | 0.01/-                      | 1.0 Pineapples                    | 0.01/-                      | 0.3 Milk and milk                 | 0.02/-                      | 0.3 Milk and milk products: Cattle | 0.02/-                      |

#### Acute risk assessment/adults/general population

| Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Commodities | pTMRL/threshold MRL (mg/kg) |
|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|
| 0.5 Apple juice                   | 0.01/-                      | 0.5 Orange juice                  | 0.01/-                      | 0.1 Apple juice                   | 0.01/-                      | 0.1 Orange juice                  | 0.01/-                      |
| 0.4 Carrot, juice                 | 0.01/-                      | 0.4 Bread/pizza                   | 0.01/-                      | 0.0 Wine                          | 0.01/-                      | 0.0 Bread/pizza                   | 0.01/-                      |
| 0.3 Grape juice                   | 0.01/-                      |                                  |                             | 0.0 Pineapples preserved          | 0.01/-                      |                                  |                             |
| 0.2 Peach juice                   | 0.01/-                      |                                  |                             |                                  |                             |                                  |                             |

| No of critical MRLs (IESTI 1)     | ---                         | No of critical MRLs (IESTI 2)     | ---                         |
|-----------------------------------|-----------------------------|-----------------------------------|-----------------------------|

#### Processed commodities

| Highest % of ARfD/ADI Processed commodities | pTMRL/threshold MRL (mg/kg) | Highest % of ARfD/ADI Processed commodities | pTMRL/threshold MRL (mg/kg) |
|---------------------------------------------|-----------------------------|---------------------------------------------|-----------------------------|
| 0.5 Orange juice                            | 0.01/-                      | 0.5 Apple juice                             | 0.01/-                      |
| 0.4 Carrot, juice                           | 0.01/-                      | 0.4 Bread/pizza                             | 0.01/-                      |
| 0.3 Grape juice                             | 0.01/-                      | 0.3 Milk and milk                           | 0.02/-                      |
| 0.2 Peach juice                             | 0.01/-                      | 0.2 Pineapples preserved                    | 0.01/-                      |

### Conclusion:

For Fenbutatin oxide, 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 non-processed commodity.

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

* 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.

*** pTMRL: provisional temporary MRL for unprocessed commodity.

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### Appendix B – Used compound codes

| Code/trivial name                                        | Chemical name/SMILES notation | Structural formula |
|----------------------------------------------------------|-------------------------------|--------------------|
| Fenbutatin oxide                                         | bis[tris(2-methyl-2-phenylpropyl)tin] oxide | ![Fenbutatin oxide](image) |
| Di-hydroxy fenbutatin oxide                              | dihydroxyfenbutatin oxide tetrakis(2-methyl-2-phenylpropyl)distannoxane-1,3-diol | ![Di-hydroxy fenbutatin oxide](image) |
| SD 31723                                                 | tetrakis(2-methyl-2-phenylpropyl)distannoxane-1,3-diol | ![Di-hydroxy fenbutatin oxide](image) |
| SD 33608                                                 | hydroxy(2-methyl-2-phenylpropyl)stannanone | ![SD 33608](image) |

SMILES: simplified molecular-input line-entry system.