Review of the existing maximum residue levels for penflufen 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 penflufen. To assess the occurrence of penflufen residues in plants, processed commodities, rotational crops and livestock, EFSA considered the conclusions derived in the framework of Regulation (EC) No 1107/2009 and Commission Regulation (EU) No 188/2011, as well as the European authorisations reported by Member States (including the supporting residues data). Based on the assessment of the available data, MRL proposals were derived and a consumer risk assessment was carried out. Although no apparent risk to consumers was identified, some information required by the regulatory framework was missing. Hence, the consumer risk assessment is considered indicative only and the MRL proposal for potatoes derived by EFSA still requires further consideration by risk managers.

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Keywords: penflufen, MRL review, Regulation (EC) No 396/2005, consumer risk assessment, fungicide

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Summary

Penflufen was approved on 1 February 2014 by means of Commission Implementing Regulation (EU) No 1031/2013 under Regulation (EC) No 1107/2009 as amended by Commission Implementing Regulations (EU) No 540/2011, 541/2011 and 2018/185.

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 15 January 2018, EFSA initiated the collection of data for this active substance. In a first step, Member States were invited to submit by 15 February 2018 their national Good Agricultural Practices (GAPs) in a standardised way, in the format of specific GAP forms, allowing the designated rapporteur Member State (RMS), Poland, to identify the critical GAPs in the format of a specific GAP overview file. Subsequently, Member States were requested to provide residue data supporting the critical GAPs, within a period of 1 month, by 22 May 2018. On the basis of all the data submitted by Member States and by the EU Reference Laboratories for Pesticides Residues (EURL), EFSA asked the RMS to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report. The PROFile and evaluation report were provided by the RMS to EFSA on 7 August 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.

Based on the information provided by the RMS, Member States and the EURL, and taking into account the conclusions derived by EFSA in the framework of Regulation (EC) No 1107/2009 and Commission Regulation (EU) No 188/2011, EFSA prepared in June 2019 a draft-reasoned opinion, which was circulated to Member States for consultation via a written procedure. Comments received by 26 July 2019 were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

The metabolism of penflufen in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement and risk assessment can be proposed as penflufen (sum of isomers) noting that the residue definitions for rotational crops are still open pending the requirement of a photolysis study of penflufen in soil and on the magnitude of metabolites (conjugated metabolite M01 and metabolites M63 and M65) in rotational crop field trials.

Residue definitions for processed commodities are not required since residues above the limit of quantification (LOQ) in seed potatoes are not expected and the tentative consumer risk assessment was below the trigger value.

Stability of penflufen and its metabolites M01 and conjugates (M03, M04), M49, M58 and M64 was demonstrated in high water, high acid, high oil, high protein and dry/high starch content commodities for a period of at least 26 months at \(-18^\circ\mathrm{C}\).

Fully validated analytical methods are available for the enforcement of the proposed residue definition in all matrices at the LOQ of 0.01 mg/kg. According to the EURLs, the LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses.

Available residue trials data were considered sufficient to derive an MRL proposal as well as risk assessment values for the commodity under evaluation.

Penflufen 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 dry matter (DM), further investigation of residues as well as the setting of MRLs in commodities of animal origin is unnecessary.

The metabolism of penflufen residues in livestock was investigated in lactating goats and laying hens at dose rates covering the maximum dietary burdens calculated in this review. Considering the authorised use assessed in this review, the calculated dietary burdens for all groups of livestock were below the trigger value of 0.1 mg/kg DM, so there is currently no need for a further investigation of residues or to derive a residue definition or to establish MRLs for commodities of animal origin. According to the EURLs, a LOQ of 0.01 mg/kg for penflufen in animal commodities is achievable by using the QuEChERS method in routine analyses (EURL, 2018).

Chronic and acute consumer exposure resulting from the authorised use reported in the framework of this review was calculated using revision 2 of the EFSA PRIMo.
The highest chronic exposure was calculated for NL child, representing 0.1% of the acceptable daily intake (ADI), and the highest acute exposure was calculated for potatoes, representing 0.3% of the acute reference dose (ARFD). Although uncertainties remain due to the data gaps identified for toxicological information relating to the presence of unidentified human metabolites and to rotational crops, this indicative exposure calculation did not indicate a risk to consumer’s health.

In addition, the potential preferential metabolism/degradation of each enantiomer of penflufen in animals and plants was not investigated in the studies submitted in the dossier and was therefore not considered. EFSA notes that in view of the large margin of safety in the exposure calculations, the potential change of isomer ratios in the final residues is not expected to be of concern for the authorised use reported in the framework of this review. In case future uses of penflufen would lead to a higher consumer exposure, further information regarding the impact of plant and/or livestock metabolism on the isomer ratio might be required (EFSA, 2019c).
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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 penflufen was approved on 1 February 2014 by means of Commission Implementing Regulation (EU) No 1031/2013\(^3\) under Regulation (EC) No 1107/2009\(^4\) as amended by Commission Implementing Regulations (EU) No 540/2011\(^5\), 514/2011\(^6\) and 2018/185\(^7\), EFSA initiated the review of all existing MRLs for that active substance.

By way of background information, in the framework of Commission Regulation (EU) No 188/2011\(^8\), Penflufen was evaluated by the United Kingdom, designated as rapporteur Member State (RMS). 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 conclusion (EFSA, 2012). It was a specific provision of the approval that only uses to treat seed potato tubers before or during planting may be authorised, limited to one application every third year on the same field. Subsequently, in the framework of Regulation (EC) No 1107/2009, the RMS (UK) received an application from Bayer CropScience AG for amendment to the conditions of approval of the active substance penflufen to lift the restriction and allow seed treatment applications on barley, conventional and hybrid seeds being drilled only once every 3 years. Following the peer review on the evaluation of the RMS (EFSA, 2016), the conditions of the approval of penflufen were amended by Commission Implementing Regulation (EU) No 2018/185: only uses to treat seeds or other propagating materials before or during sowing or planting, may be authorised, limited to one application every third year on the same field.

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. It should be noted, however, that, in the framework of Regulation (EC) No 1107/2009, 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 Regulation (EC) No 1107/2009 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 animal commodities;
- the environmental fate and behaviour in the environment;
- the occurrence in feed and food of plant and animal origin;
- nature of residues in rotational crops;
- effects on plants;
- effects on有益微生物和有益生物;
- effects on beneficial organisms;
- effects on non-target plants, including non-target flowering plants and non-target trees;
- effects on birds;
- effects on fish and aquatic life;
- effects on terrestrial life.

\(^1\) 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 Implementing Regulation (EU) No 1031/2013 of 24 October 2013 approving the active substance penflufen, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011. OJ L 283, 25.10.2013, p. 17–21.

\(^4\) 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 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.

\(^6\) Commission Implementing Regulation (EU) No 541/2011 of 1 June 2011 amending Implementing Regulation (EU) No 540/2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards the list of approved active substances. OJ L 153, 11.6.2011, p. 187–188.

\(^7\) Commission Implementing Regulation (EU) 2018/185 of 7 February 2018 amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance penflufen. OJ L 34, 8.2.2018, p. 13–15.

\(^8\) Commission Regulation (EU) No 188/2011 of 25 February 2011 laying down detailed rules for the implementation of Council Directive 91/414/EEC as regards the procedure for the assessment of active substances which were not on the market 2 years after the date of notification of that Directive. OJ No L 53, 26.2.2011, p. 51–55.
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 15 January 2018, EFSA initiated the collection of data for this active substance. In a first step, Member States (MS) were invited to submit by 15 February 2018 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, 13 MSs provided feedback on their national authorisations of penflufen. Based on the GAP data submitted, Poland, the designated RMS in the MRL review was asked to identify the critical GAPs to be further considered in the assessment, in the format of a specific GAP overview file. Subsequently, in a second step, MSs were requested to provide residue data supporting the critical GAPs by 22 May 2018.

On the basis of all the data submitted by MSs and the EU Reference Laboratories for Pesticides Residues (EURL), EFSA asked Poland to complete the PROFile and to prepare a supporting evaluation report. The PROFile and the supporting evaluation report were submitted to EFSA on 7 August 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 June 2019 a draft-reasoned opinion, which was circulated to MSs for commenting via a written procedure. All comments received by 26 July 2019 were considered by EFSA during the finalisation of the reasoned opinion.

The evaluation report submitted by the RMS (Poland, 2018), taking into account also the information provided by MSs 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, 2019a) and the Member States consultation report (EFSA, 2019b). 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 EFSA Pesticide Residues Intake Model (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

Penflufen is the ISO common name for 2’-((RS)-1,3-dimethylbutyl)-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide (IUPAC).

The chemical structure of the active substance and its main metabolites are reported in Appendix F. For penflufen, 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 penflufen 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 penflufen currently authorised within the EU as submitted by the MSs 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 penflufen are given in Appendix A. The RMS did not report any use authorised in third countries that might have a significant impact on international trade.
Assessment

EFSA has based its assessment on the following documents:

- the PROFile submitted by the RMS;
- the evaluation report accompanying the PROFile (Poland, 2018);
- the draft assessment report (DAR) and its revisions prepared under Commission Regulation (EU) No 188/2011 and Regulation (EC) No 1107/2009 (United Kingdom, 2011, 2015, 2016);
- the conclusions on the peer review of the pesticide risk assessment of the active substance penflufen (EFSA, 2012, 2016);

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 546/2011 and the currently applicable guidance documents relevant for the consumer risk assessment of pesticide residues (European Commission, 1997a–g, 2000, 2010a,b, 2017a; 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 penflufen was investigated in roots, cereals and oilseeds (potatoes, wheat and soybean) when used as a seed treatment and in roots and cereals (potatoes, paddy rice) when used as a soil treatment (United Kingdom, 2011) and assessed in the framework of the peer review (EFSA, 2012). Two studies were performed in each crop to account for labelling either on the pyrazole ring or the phenyl ring. An overview of the studies is provided (Appendix B.1.1.1).

After one seed application of pyrazole-labelled penflufen 190 g a.s./ha (1.9N of critical GAP (cGAP) rate) on potatoes and of 530 g a.s./ha (5.3N rate) for the in-furrow treatment, the major component identified in the potatoes was penflufen, representing 20.1–28.2% of the total radioactive residues (TRR) while five metabolites, penflufen-3-hydroxy-butyl (M01), penflufen-3-hydroxy-butyl-glucoside (M03), penflufen-3-hydroxy-butyl-malonyl-glucoside (M04), penflufen-glutathione (M48), penflufen-cystein ((M53), each representing less than 10% of the TRR), were present in total at 18.9–32.0% TRR (United Kingdom, 2011). Residue levels of penflufen and the metabolites (each individual metabolite was below 0.01 mg eq/kg) in potatoes were 0.016–0.036 mg eq/kg and 0.024–0.025 mg eq/kg, respectively (United Kingdom, 2011).

After one seed application of phenyl-labelled penflufen 166 g a.s./ha (1.7N rate) on potatoes and of 544 g a.s./ha (5.4N rate) for the in-furrow treatment, the major component identified in the potatoes was penflufen, representing 18.9–21.5% of the TRR while five metabolites (M01, M03, M04, M48 and M53) each representing less than 10% of the TRR, except metabolite M01 in the seed application (19% TRR (free M01 with 12% TRR and conjugated M01 with 6.8% TRR (M03 (3.2% TRR; M04 3.6% TRR)) were present at 23.3–25.2% TRR (United Kingdom, 2011). Residue levels of penflufen and the metabolites (each individual metabolite was below 0.01 mg eq/kg, except metabolite M48 (0.011 mg eq/kg)) in potatoes were 0.003–0.021 mg eq/kg and 0.005–0.025 mg eq/kg, respectively (United Kingdom, 2011).

The metabolic pathway for both labels in potatoes followed two routes. In one route, the aliphatic side chain is hydroxylated to penflufen-3-hydroxy-butyl (M01). The hydroxyl group is conjugated with glucose and malonic acid to penflufen-3-hydroxy-butyl-glucoside (M03) and penflufen-3-hydroxy-butyl-malonyl-glucoside (M04). In the other route, glutathionylation of the pyrazole moiety leads to penflufen-glutathione (M48). Subsequent degradation of the glutathione moiety results in penflufen-cystein (M53).

In spring wheat, metabolism of pyrazole- and phenyl-labelled penflufen was studied, after one seed application of 12 or 117 g a.s./ha, and of 10.4 or 120 g a.s./ha, respectively. Since the total radioactive residues in wheat grain were very low (< 0.01 mg/kg), no further metabolites characterisation or

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9 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.
identification was attempted. Penflufen was detected in wheat forage and hay (up to 1.3–1.4% TRR (< 0.001–0.001 mg eq/kg)) and not in wheat straw. In wheat straw, the parent compound was extensively metabolised mainly into metabolite M01 both in its free and conjugated forms (M03, M04 and M05) (up to 5% (0.01 mg eq/kg) and 50% TRR (0.1 mg eq/kg, respectively) (United Kingdom, 2011; EFSA, 2012).

In rice, metabolism of phenyl- and pyrazole-labelled penflufen was studied, after one soil application of 500–520 g a.s./ha, respectively, on sandy loam soil in glasshouse paddy conditions. The major component identified in the rice kernels was penflufen, representing 20% and 31.3% of the TRR while metabolite M01 was present at 20.1% and 22.9% TRR, respectively. Residue levels of penflufen and metabolite M01 in the rice were 0.004–0.005 mg eq/kg in both labels, respectively (United Kingdom, 2011).

In soybeans, metabolism of pyrazole and phenyl-labelled penflufen was studied, after one soil application of 5.8 and 51 g a.s./ha and of 5.9 and 52 g a.s./ha, respectively, on sandy loam soil in glasshouse conditions. The main components identified in the soybean seeds were metabolites penflufen-desmethyl-dicarboxylic acid (M63) (65.1% TRR, 0.016 mg e.q./kg) resulting from the cleavage of the parent compound at the carboxamide linkage, along with metabolite penflufen homoglutathione (M49) (up to 77.3% TRR, 0.009 mg e.q./kg). Metabolite M53 was significant in soybean forage with 10–13% TRR (0.02–0.023 mg eq/kg). Penflufen or metabolite M01 was not detected and conjugate M04 was below 10% TRR (below 0.012 mg eq/kg), however, was highly significant in soybean hay with 37–38% TRR (0.009–0.011 mg eq/kg) (United Kingdom, 2011; EFSA, 2012).

It can be concluded from the available metabolism studies that penflufen and the metabolite M01 (free and conjugated) were the predominant compounds of the total residues in potato tubers, spring wheat and rice, whereby in soybean seeds, a different metabolism was observed with the main metabolites M49 and M63. Since only uses on potatoes are authorised, the metabolism data are considered sufficient to support the authorised use.

1.1.2. Nature of residues in rotational crops
Penflufen is authorised on crops that may be grown in rotation. The field DT90 reported in the soil degradation studies evaluated in the framework of the peer review was 1,521 days (EFSA, 2012). Therefore, an investigation of residues in rotational crops following single and multiannual application is required.

The metabolism and distribution of penflufen in rotational crops (small grain (spring wheat), oilseeds (soybeans), root and tuber vegetables (turnips) and leafy crops (swiss chard)) were investigated in three confined studies with target application rates of 10 g a.s./ha (0.1N) or 500 g a.s./ha (5N) and were assessed during the peer review (United Kingdom, 2011; EFSA, 2012).

In two confined rotational crop studies, penflufen was radiolabelled on the pyrazole or phenyl ring and applied onto bare soil at rates of 532 and 534 g a.s./ha, respectively. Crops were planted at nominal plant back intervals (PBI) of 30, 157 and 377 days or 30, 156 and 376 days after treatment (DAT). Crops planted at each interval consisted of root and tuber vegetables (turnips), small grain (spring wheat) and pulses and oil seeds (soybeans).

Residues in turnips (leaves and roots), wheat (grain, straw and hay), soybean (seeds, forage and hay) declined over time, while residues in wheat forage were highest in the second rotation and declined in the third. Highest levels of penflufen were observed in turnip roots (8–16% TRR; 0.001–0.009 mg eq/kg) 30 DAT and (8–14% TRR; 0.001–0.002 mg eq/kg) 377 DAT. In wheat grain and soya seeds, 30 DAT penflufen was not detected; however, significant residues of its metabolites were observed up to 377 DAT in edible parts of all rotated crops.

These confined rotational crop studies on turnips, wheat and soybean indicated that penflufen was intensively degraded and detected only in wheat straw and turnip roots (3.2% and 15.6%, respectively). Glucoside conjugated M01 accounted for 53–85% TRR in wheat grain, soybean seeds and turnip roots. However, the metabolic profile was dominated by the pyrazole-derived metabolites M58, M63, M64, M65 resulting from the cleavage of the parent molecule at the carboxamide bond, which accounted overall for up to 57% TRR in wheat grain, 83% TRR in soybean seeds and 35% TRR in turnip roots.

A third confined rotational crop study with penflufen labelled on the pyrazole or phenyl ring with an application rate of 10 g a.s./ha onto soil, respectively, was assessed during the peer review noting that it represented only 0.1N of the critical GAP rate in line with the GAP assessed in this Art. 12 review. Crops were planted at nominal PBIs of 30, 139 and 287 DAT and consisted of leafy crops (swiss chard), root and tuber vegetables (turnips) and small grain (spring wheat). Samples where the TRR in
the raw agricultural commodity (RAC) was below limit of quantification (LOQ) were not further characterised. Otherwise, samples were extracted and characterised. TRR levels for both labels were low and maximum values ranged from 0.058 to 0.059 mg eq/kg in wheat straw in the first rotation. Residues declined generally in subsequent wheat rotations and the radioactivity of the second and third rotations of swiss chard and turnips were not determined since TRRs were already below 0.01 mg eq/kg in the first rotation.

During the peer review, the predominance of the pyrazole-derived metabolites in the rotational crop study when compared to the primary crop studies was highlighted and considered potentially treatment related because penflufen was applied to bare soil without soil incorporation. Therefore, potentially photolytic degradation could have resulted in the formation of the pyrazole metabolites followed by plant uptake. However, no soil photolysis study was available to substantiate such a hypothesis and a data gap was flagged (EFSA, 2012).

Additional information was not made available during this review. Therefore, a soil photolysis study is still required (data gap).

1.1.3. Nature of residues in processed commodities

Since in all commodities residues were below 0.1 mg/kg and the total theoretical maximum daily intake is as well anticipated to be below 10% of the acceptable daily intake (ADI), an investigation of the nature of residues in processed commodities is in principle not required.

Nevertheless, studies investigating the nature of residues in processed commodities were provided and assessed during the peer review (EFSA, 2012). Two studies were conducted with penflufen and the metabolite M01, both radiolabelled on the pyrazole ring, simulating representative hydrolytic conditions for pasteurisation (20 min at 90°C, pH 4), boiling/brewing/baking (60 min at 100°C, pH 5) and sterilisation (20 min at 120°C, pH 6).

Penflufen and its metabolite M01 were found to be stable under standard hydrolysis conditions of pasteurisation, baking/brewing/baking and sterilisation (United Kingdom, 2011; EFSA, 2012).

It is noted that the hydrolysis studies with both analytes were performed with the pyrazole label only and no representative processing studies were available with the phenyl label. This is considered acceptable since the pyrazole-labelled test items were resistant to hydrolysis, and therefore, no phenyl-specific hydrolytic products are expected.

1.1.4. Methods of analysis in plants

During the peer review, a hyphenated analytical method based on LC-MS/MS detection of penflufen was validated in dry, high water and acid commodities (head lettuce, potato (tuber), dry bean (seed), carrot (leaf and root), barley (green material, grain and straw) and orange (fruit)), with a LOQ of 0.01 mg/kg.

The analytical method provides information on two separate MS transitions (i.e. for quantification and confirmation) and as such, is deemed to be highly specific. The primary method is supported by a confirmatory method and an independent laboratory validation (ILV) performed on potato, dry bean, barley and orange.

Sunflower seeds were also analysed for penflufen residues although low recoveries were generally observed. Therefore, the method is not suitable for the detection of penflufen in oily matrices (EFSA, 2012).

During the completeness check, the EURLs provided a QuEChERS and a QuOil multi-residue analytical method using LC-MS/MS and LC-QqQ-MS/MS, with a LOQ of 0.01 mg/kg for the routine analysis of penflufen in high water and high acid content commodities, dry and of high oil content commodities, respectively (EURLs, 2018).

1.1.5. Stability of residues in plants

The storage stability of penflufen and its metabolites M01, M03, M04, M49, M58 and M64 were investigated in the framework of the peer review (EFSA, 2012).

In high water, high acid, high protein, high oil and dry/high starch content commodities, the available studies demonstrate stability for penflufen and its metabolites M01 and conjugates (M03, M04), M49, M58 and M64 for a period of at least 26 months when stored at –18°C (Appendix B.1.1.2).
1.1.6. Proposed residue definitions

Penflufen was considered a valid marker of the total residue in root and tuber vegetables, and the residue definition for monitoring was limited to the parent compound only (sum of isomers).

For risk assessment, since metabolite M01 was recovered at comparable levels as the parent compound in potato tubers after seed and in-furrow treatments, it was initially suggested during the peer review to include this metabolite which is toxicologically relevant in the residue definition. However, in the GAP compliant residue trials on potato, metabolite M01 was not detected. Therefore, it was concluded to limit the residue definition for risk assessment to the parent penflufen (sum of isomers) for root and tuber vegetables (seed and in-furrow soil treatments only) (EFSA, 2012).

During the peer review, it was subsequently proposed to adopt for cereals the residue definition for monitoring and risk assessment (proposed initially for root crops) (EFSA, 2016). The proposed residue definitions of the peer review for root and tuber and cereal crops as penflufen (sum of isomers) is supported in this review.

It is noted that data gaps and concerns in the toxicology section identified during the peer review are still open and could not be finalised (EFSA, 2016). In particular, data gap identified for repeated dose toxicity testing on metabolite (M01) is considered relevant in the framework of this Art. 12 review since M01 might be a relevant metabolite.

Furthermore, data gaps regarding rotational crop metabolism (photolysis soil study (Section 1.1.2) and field trials covering the calculated plateau concentration of penflufen in soil to determine residue levels of conjugated metabolite M01 and metabolites M63 and M65 are still needed (Section 1.2.2). Therefore, a residue definition for rotational crops cannot be concluded for the time being.

For processed commodities, residue definitions are not required because studies on processed commodities are not triggered as processing is not expected to change the nature of the residues.

An analytical method for the enforcement of the proposed residue definition at the LOQ of 0.01 mg/kg in water, high acid and dry matrices is available (EFSA, 2012). According to the EURLs, the LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses (EURLs, 2018).

In addition, EFSA emphasises that the above studies do not investigate the possible impact of plant metabolism on the isomer ratio of penflufen and notes that in view of the large margin of safety in the exposure calculation, the potential change in isomer ratios in the final residue is not expected of concern for the authorised use in the framework of this review. In case future uses of penflufen would lead to a higher consumer exposure, further information regarding the impact of plant and/or livestock metabolism on the isomer ratio might be required (EFSA, 2019c).

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

To assess the magnitude of penflufen residues resulting from the reported GAPs, EFSA considered all residue trials reported by the RMS in its evaluation report (Poland, 2018) as well as the residue trials evaluated in the framework of the peer review (United Kingdom, 2011; EFSA, 2012). 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 was evaluated in accordance with the European guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs (European Commission, 2017).

Sufficient residue trials on potatoes in Northern Europe were provided and considered acceptable to derive a MRL at the LOQ of 0.01 mg/kg. It can be concluded that the available residue trials were considered sufficient to derive a MRL proposal as well as risk assessment values for the commodity under evaluation, taking note of the following considerations:

- The number of seven residue trials supporting the northern outdoor GAP for potatoes is not compliant with the data requirements for this crop. However, the reduced number of residue trials is considered acceptable in this case because all results were below the LOQ. Further residue trials are therefore not required.
1.2.2. Magnitude of residues in rotational crops

Considering the cGAPs reported in this review (one application at BBCH 0–3 at a rate of 100 g a.s./ha), assuming a soil density of 1.5 g/L, soil depth of 5 cm, no crop interception and considering the double first-order in parallel (DFOP) soil dissipation kinetics, $K_1$: 0.0373 day$^{-1}$, $K_2$: 0.0012 day$^{-1}$, g: 0.5079, the plateau concentration derived in soil, taking into account accumulation over the years, is 0.145 mg/kg (EFSA, 2012, 2016). The PEC over 20 cm that is usually used when cultivation will occur before planting following crops is 0.036 mg/kg in a crop failure situation but would be 0.012 mg/kg if the following crop was planted following harvest of the primary crop and subsequent soil cultivation.

Based on reported residue concentrations in the rotational confined crop study on turnips, wheat and soybeans, it can be concluded that penflufen residue levels in edible parts of rotational commodities above the LOQ of 0.01 mg/kg are not expected considering the overdosing factor (approximately 5N compared to the primary crop dose rate (532–534 g/ha applied) and approximately 15N compared to the accumulated soil residues at following crop planting calculated at 0.012 mg/kg), provided that penflufen is applied in compliance with the GAP reported in Appendix A.

During the peer review rotational crop field trials conducted on carrot, lettuce and wheat/barley at an application rate of 100 g a.s./ha were considered underdosed in respect of the calculated plateau concentration in soil. It was further noted that only free M01 was analysed since the analytical method did not contain a hydrolysis step and the study did not address the case of soybean in rotation where significant residues of M01 (free and conjugated), M49, M63, M64 and M65 were expected (EFSA, 2012).

A new field rotational crop study was available for this review (Poland, 2018). Unlabelled penflufen was applied at 240 g a.s./ha during planting of potatoes. Rotational crops (leafy vegetable (lettuce), roots (turnips), cereals (winter barley)) were planted 25 ± 5 DAT, 90–200 DAT and 270–364 DAT whereby the last interval was cancelled because no residues were found in previous rotations.

Rotational crops were sampled between 66-80 and 160-174 DAT for lettuce, between 186-200 DAT for turnips and between 238-310 and 367-439 DAT for winter barley. Penflufen and metabolites M01 (free), M49, M58 and M64 levels were all below the LOQ for lettuce heads, winter barley green material, grain and straw, turnip leaves and roots.

Information on the soil used, and the fact that the residue was incorporated was provided; however, the penflufen soil concentration in the root zone was not available. Nevertheless, considering that 240 g penflufen/ha were applied directly to soil (2.2N compared to the primary crop dose rate and 6.1N compared to the accumulated soil residues at following crop planting calculated at 0.012 mg/kg) and assuming the behaviour of the isomers is equivalent in soil, it is concluded that the plateau concentration expected after use of penflufen at the critical GAP rate is covered by these studies.

The available studies indicate that an application of penflufen according to cGAP conditions would not lead to a significant uptake of penflufen and its metabolite M01 (free), M49, M58 and M64 in the succeeding crops investigated which notably did not include an oilseed.

Nevertheless, the data gap identified during the peer review related to additional metabolites (conjugated metabolite M01 and metabolites M63 and M65) which were not investigated in the available study, remains open. Consequently, additional field rotational crops studies covering the most critical GAP currently authorised on potatoes and the calculated PEC soil are still required. In the meanwhile, MSs granting authorisations for penflufen should take appropriate risk mitigation measures (e.g. specify deep ploughing (more than 20 cm soil mixing) to dilute soil concentrations) in order to avoid the presence of significant residues in rotational crops.

1.2.3. Magnitude of residues in processed commodities

Studies investigating the effect of residues of penflufen in processed commodities are not available and are not required as they are not expected to affect the outcome of the risk assessment because stability of penflufen and metabolite M01 was demonstrated under standard hydrolysis conditions (see Section 1.1.3).

However, if more robust processing factors were to be required by risk managers, particularly for enforcement purposes, additional processing studies would be needed.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive an MRL proposal as well as risk assessment values for potatoes.
Residue definitions for rotational crops cannot be derived and it cannot be concluded whether MRLs for rotational crops are required. Nevertheless, specific MRLs in rotational crops are not needed, provided MSs will take adequate risk mitigation measures (e.g. specify deep ploughing (more than 20 cm soil mixing) to dilute soil concentrations) to avoid significant residues to occur in rotational crops.

2. Residues in livestock

Penflufen is authorised for use on potatoes 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.1.

Considering the authorised use assessed in this review, the calculated dietary burdens for all groups of livestock were below the trigger value of 0.1 mg/kg dry matter (DM), so there is no need for a further investigation of residues or to derive a residue definition or to establish MRLs for commodities of animal origin.

It has to be noted that while residue levels above the LOQ are unlikely to occur in succeeding crops, only primary crops have been taken into account to calculate the dietary burden; however, it must be noted that the available rotational crop studies do not cover all relevant metabolites and that the residue definition for rotational crops is still pending.

The metabolism of penflufen residues in livestock was investigated in lactating goats and laying hens at dose rates covering the maximum dietary burdens calculated in this review. In these studies, penflufen was radiolabelled in the pyrazole and phenyl ring of the molecule. A single metabolism study with phenyl-labelled penflufen in fish was performed to unagreed guidelines and was therefore not evaluated during the peer review (United Kingdom, 2011; EFSA, 2012).

The study performed on lactating goats indicates a significant transfer of pyrazole-labelled penflufen residues to liver, kidney, fat and milk and an insignificant transfer of residues to muscle. Highest residue levels were found in liver (0.319 mg eq./kg), kidney and milk (0.084 mg eq./kg) and fat (0.013 mg eq./kg) whilst transfer to muscle tissues (< 0.01 mg eq./kg) was limited. For the phenyl label, significant residues were reported in all tissues. Highest residue levels were found in liver (0.297 mg eq./kg), kidney (0.126 mg eq./kg) and milk (0.097 mg eq./kg) and significant levels in fat (0.018 mg eq./kg) and muscle tissues (0.012 mg eq./kg).

The study performed on laying hens indicates a significant transfer of residues to all tissues. For pyrazole-labelled penflufen, highest residue levels were found in liver (0.636 mg eq./kg), kidney (0.378 mg eq./kg) and significant levels in eggs (0.160 mg eq./kg), skin without fat (0.138 mg eq./kg), subcutaneous fat (0.103 mg eq./kg) and muscle tissues (0.047 mg eq./kg). For the phenyl label, highest residue levels were found in liver (0.619 mg eq./kg), kidney (0.401 mg eq./kg) and significant levels in eggs (0.194 mg eq./kg), skin without fat (0.108 mg eq./kg), subcutaneous fat (0.098 mg eq./kg) and muscle tissues (0.045 mg eq./kg).

Metabolism in lactating goats and laying hen is essentially similar. The metabolic pathway elucidated were N-demethylation, hydroxylation (and subsequent oxidation to ketone or carboxylic acid groups) and conjugation with glucuronic acid. Similar metabolism is seen in the lactating goat and in rat, and therefore, additional studies in pigs are not required (United Kingdom, 2011).

EFSA concludes that the metabolism of penflufen in livestock is adequately elucidated; however notably, a residue definition for rotational crops could not be derived and the magnitude of residues in rotational crops could not be concluded upon (Section 1.2.2). During the peer review, it was highlighted that a reliable residue definition based on the available ruminant and poultry metabolism studies could not be derived and that the setting of a robust residue definition should be considered pending the outcome of the identified data gap on rotational crops (EFSA, 2012). This conclusion is still valid for this review since there are still remaining data gaps in the available rotational crop studies.

An analytical method for the enforcement of the proposed residue definition was not provided. According to the EURLs, a LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses (EURL, 2018).

The storage stability of penflufen in animal matrices was not investigated and is not required (United Kingdom, 2011).
3. Consumer risk assessment

In the framework of this review, only the use of penflufen reported by the RMS following consultation of MSs and their confirmation in Appendix A were considered.

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 those commodities where an 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 penflufen, derived by EFSA (2012). The highest chronic exposure was calculated for NL child, representing 0.1% of the ADI, and the highest acute exposure was calculated for potatoes, representing 0.3% of the acute reference dose (ARfD).

This calculation is to be regarded as provisional pending information on toxicology as identified during the peer review and on a residue definition for rotational crops and clarification on a need for setting MRLs in rotational crops.

Furthermore, the potential preferential metabolism/degradation of each enantiomer of penflufen in animals and plants was not investigated in the studies submitted in the dossier and was therefore not considered.

EFSA notes that in view of the large margin of safety in the exposure calculations, the potential change of isomer ratios in the final residues is not expected to be of concern for the authorised use assessed in the framework of this review. In case future uses of penflufen would lead to a higher consumer exposure, further information regarding the impact of plant and/or livestock metabolism on the isomer ratio might be required (EFSA, 2019c).

Conclusions

The metabolism of penflufen in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement and risk assessment can be proposed as penflufen (sum of isomers) noting that the residue definitions for rotational crops are still open pending the requirement of a photolysis study of penflufen in soil and on the magnitude of metabolites (conjugated metabolite M01 and metabolites M63 and M65) in rotational crop field trials.

Residue definitions for processed commodities are not required since residues above the LOQ in seed potatoes are not expected and the tentative consumer risk assessment was below the trigger value.

Stability of penflufen and its metabolites M01 and conjugates (M03, M04), M49, M58 and M64 was demonstrated in high water, high acid, high oil, high protein and dry/high starch content commodities for a period of at least 26 months at \(-18^\circ\text{C}\).

Fully validated analytical methods are available for the enforcement of the proposed residue definition in all matrices at the LOQ of 0.01 mg/kg. According to the EURLs, the LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses.

Available residue trials data were considered sufficient to derive an MRL proposal as well as risk assessment values for the commodity under evaluation.

Penflufen 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 unnecessary.

The metabolism of penflufen residues in livestock was investigated in lactating goats and laying hens at dose rates covering the maximum dietary burdens calculated in this review. Considering the authorised use of this review, the calculated dietary burdens for all groups of livestock were below the trigger value of 0.1 mg/kg DM, there is currently no need for a further investigation of residues or to derive a residue definition or to establish MRLs for commodities of animal origin. According to the EURLs, in animal commodities, a LOQ of 0.01 mg/kg for penflufen is achievable by using the QuEChERS method in routine analyses (EURL, 2018).

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 chronic exposure was calculated for NL child, representing 0.1% of the ADI, and the highest acute exposure was calculated for potatoes, representing 0.3% of the ARfD. Although uncertainties remain due to the data gaps identified for toxicological information relating to the presence of unidentified human metabolites and to rotational crops, this indicative exposure calculation did not indicate a risk to consumer’s health.

In addition, the potential preferential metabolism/degradation of each enantiomer of penflufen in animals and plants was not investigated in the studies submitted in the dossier and was therefore not considered. EFSA notes that in view of the large margin of safety in the exposure calculations, the potential change of isomer ratios in the final residues is not expected to be of concern for the authorised use reported in the framework of this review. In case future uses of penflufen would lead to a higher consumer exposure, further information regarding the impact of plant and/or livestock metabolism on the isomer ratio might be required (EFSA, 2019c).

**Recommendations**

MRL recommendations were derived in compliance with the decision tree reported in Appendix E of the reasoned opinion (see Table 1). The MRL values listed in the table are recommended for inclusion in Annex II (see Table 1 footnotes for details).

It is highlighted, however, that the MRL is derived based on residue results from a GAP in one climatic zone only. EFSA identified the following data gaps which are not expected to impact on the validity of the MRLs derived but which might have an impact on national authorisations:

- a photolysis study of penflufen in soil;
- rotational crop field trials on cereals, leafy vegetables, root vegetables and soybean at a dose rate covering the calculated plateau concentration of penflufen in soil to determine residue levels of conjugated metabolite M01 and metabolites M63 and M65;
- repeated dose toxicity testing on metabolite M01 for which a data gap was set during the peer review.

If the above-reported data gaps are not addressed in the future, MSs are recommended to withdraw or modify the relevant authorisations at national level. In the meanwhile, MSs granting authorisations for penflufen should take appropriate risk mitigation measures (e.g. specify deep ploughing (more than 20 cm soil mixing) to dilute soil concentrations) to avoid the presence of significant residues in rotational crops.

### Table 1: Summary table

| Code number | Commodity | Existing EU MRL (mg/kg) | Existing CXL (mg/kg) | MRL (mg/kg) | Comment |
|-------------|-----------|------------------------|---------------------|-------------|---------|
| 0211000     | Potatoes  | 0.01*                  | –                   | 0.01*       | Recommended(a) |
| –           | Other commodities of plant and/or animal origin | See Art 18(1)(b) Reg 396/2005 | – | – | 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 H-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).

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Abbreviations

a.i. active ingredient
a.s. active substance
ADI acceptable daily intake
ARfD acute reference dose
| Acronym | Description |
|---------|-------------|
| BBCH    | growth stages of mono- and dicotyledonous plants |
| bw      | body weight |
| CF      | conversion factor for enforcement residue definition to risk assessment residue definition |
| cGAP    | critical GAP |
| CXL     | codex maximum residue limit |
| DAR     | draft assessment report |
| DAT     | days after treatment |
| DM      | dry matter |
| DT₉₀    | period required for 90% dissipation (define method of estimation) |
| eq      | residue expressed as a.s. equivalent |
| EURTs   | European Union Reference Laboratories for Pesticide Residues (former CRLs) |
| FAO     | Food and Agriculture Organization of the United Nations |
| GAP     | Good Agricultural Practice |
| HPLC-MS/MS | high-performance liquid chromatography with tandem mass spectrometry |
| HR      | highest residue |
| IEDI    | international estimated daily intake |
| IESTI   | international estimated short-term intake |
| ILV     | independent laboratory validation |
| ISO     | International Organisation for Standardization |
| IUPAC   | International Union of Pure and Applied Chemistry |
| LC-MS/MS | liquid chromatography with tandem mass spectrometry |
| LOQ     | limit of quantification |
| Mo      | monitoring |
| MRL     | maximum residue level |
| MS      | Member States |
| NEU     | northern European Union |
| OECD    | Organisation for Economic Co-operation and Development |
| PBI     | plant back interval |
| PF      | processing factor |
| PHI     | preharvest interval |
| Pₚₜₒₓ | partition coefficient between n-octanol and water |
| ppm     | parts per million (10⁻⁶) |
| 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 |
| RAC     | raw agricultural commodity |
| 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 |
| WHO     | World Health Organization |

Review of the existing MRLs for penflufen
### 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 G or I(a) | Pests or group of pests controlled | Preparation Type(b) | Conc. a.s. | Method kind | Range of growth stages & season(c) | Number min–max | Interval between application (min) | a.s./hL min–max | Water L/ha min–max | Rate and unit | PHI (days)(d) | Remarks |
|-----------------------|--------------|-------------|-----------------------------------|---------------------|-----------|------------|-----------------------------------|----------------|----------------------------------|----------------|-------------------|-------------|-------------|---------|
| Potatoes              | DE           | F           | Rhizoctonia solani, silver scurf (Helminthosporium solani) | FS                  | 100 g/L   | Seed treatment – spraying | 0–3                      | 1                 | –                  | –              | –                 | n.a.        | Application before planting Max. 50 dt seed stock pro ha treated with 20 g a.i./ton applied per hectare; seed stock treatment for seed production Maximum 1 application per 3 years on the same plot |

MS: Member State.
(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).
(b): CropLife International Technical Monograph no 2, 6th Edition. Revised May 2008. Catalogue of pesticide.
(c): Growth stage range from first to last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including, where relevant, information on season at time of application.
(d): PHI: minimum pre-harvest 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(s) | Application(s) | Sampling (DAT) | Comment/source |
|-----------------------------------|---------|----------------|---------------|---------------|
| Root crops                        | Potatoes | 1 × 190 g a.i./ha | 140 | Pyrazole-3-\(^{14}\)C-labelled penflufen, seed treatment (United Kingdom, 2011) |
|                                  | Potatoes | 1 × 166 g a.i./ha | 140 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, seed treatment (United Kingdom, 2011) |
|                                  | Potatoes | 1 × 530 g a.i./ha | 140 | Pyrazole-3-\(^{14}\)C-labelled penflufen, in-furrow treatment (United Kingdom, 2011) |
|                                  | Potatoes | 1 × 544 g a.i./ha | 140 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, in-furrow treatment (United Kingdom, 2011) |
| Cereals/grass                     | Spring wheat | 1 × 12 g a.i./ha | 52, 95, 109 | Pyrazole-3-\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (52 DAT), hay (95 DAT) and 109 DAT: grain and straw (United Kingdom, 2011) |
|                                  | Spring wheat | 1 × 117 g a.i./ha | 52, 95, 109 | Pyrazole-3-\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (52 DAT), hay (95 DAT) and 109 DAT: grain and straw (United Kingdom, 2011) |
|                                  | Spring wheat | 1 × 10.4 g a.i./ha | 52, 95, 109 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (52 DAT), hay (95 DAT) and 109 DAT: grain and straw (United Kingdom, 2011) |
|                                  | Spring wheat | 1 × 120 g a.i./ha | 52, 95, 109 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (52 DAT), hay (95 DAT) and 109 DAT: grain and straw (United Kingdom, 2011) |
|                                  | Paddy rice | 1 × 520 g a.i./ha | 108 | Pyrazole-3-\(^{14}\)C-labelled penflufen, in-furrow treatment (United Kingdom, 2011) |
|                                  | Paddy rice | 1 × 500 g a.i./ha | 108 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, in-furrow treatment (United Kingdom, 2011) |
| Pulses/oilseeds                  | Soybeans | 1 × 5.8 g a.i./ha | 29, 67, 116 | Pyrazole-3-\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (29 DAT), hay (67 DAT) and 116 DAT: seeds and mature plant (United Kingdom, 2011) |
|                                  | Soybeans | 1 × 51 g a.i./ha | 29, 67, 116 | Pyrazole-3-\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (29 DAT), hay (67 DAT) and 116 DAT: seeds and mature plant (United Kingdom, 2011) |
|                                  | Soybeans | 1 × 5.9 g a.i./ha | 30, 68, 110 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (30 DAT), hay (68 DAT) and 110 DAT: seeds and mature plant (United Kingdom, 2011) |
|                                  | Soybeans | 1 × 52 g a.i./ha | 30, 68, 110 | Phenyl-UL-\(^{13}\)C/\(^{14}\)C-labelled penflufen, seed treatment, sampling of forage (30 DAT), hay (68 DAT) and 110 DAT: seeds and mature plant (United Kingdom, 2011) |
## Rotational crops (available studies)

| Crop groups       | Crop(s)                                      | Application(s) | PBI (DAT) | Comment/source                                                                 |
|-------------------|----------------------------------------------|----------------|-----------|-------------------------------------------------------------------------------|
| Root/tuber crops  | Turnips (leaves, roots)                      | 532 g a.i./ha  | 30, 157, 377 | Pyrazole-3-14C-labelled penflufen (United Kingdom, 2011)                      |
|                   | Turnips (leaves, roots)                      | 534 g a.i./ha  | 30, 156, 376 | Phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011)                  |
|                   | Turnips (leaves, roots)                      | 10 g a.i./ha   | 30, 139, 287 | Pyrazole-3-14C-labelled penflufen or phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011) |
| Leafy crops       | Swiss chard (immature and mature plant)       | 10 g a.i./ha   | 30, 139, 287 | Pyrazole-3-14C-labelled penflufen or phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011) |
|                   | Swiss chard (immature and mature plant)       | 10 g a.i./ha   | 30, 139, 287 | Pyrazole-3-14C-labelled penflufen or phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011) |
| Cereal (small grain) | Wheat (forage, hay, straw, grain)            | 532 g a.i./ha  | 30, 157, 377 | Pyrazole-3-14C-labelled penflufen (United Kingdom, 2011)                      |
|                   | Wheat (forage, hay, straw, grain)            | 534 g a.i./ha  | 30, 156, 376 | Phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011)                  |
|                   | Wheat (forage, hay, straw, grain)            | 10 g a.i./ha   | 30, 139, 287 | Pyrazole-3-14C-labelled penflufen or phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011) |
| Oil seeds         | Soybean (forage, hay, seeds)                 | 532 g a.i./ha  | 30, 157, 377 | Pyrazole-3-14C-labelled penflufen (United Kingdom, 2011)                      |
|                   | Soybean (forage, hay, seeds)                 | 534 g a.i./ha  | 30, 156, 376 | Phenyl-UL-13C6/14C-labelled penflufen (United Kingdom, 2011)                  |

## Processed commodities (hydrolysis study)

| Conditions                      | Stable? | Comment/Source                                                                 |
|---------------------------------|---------|-------------------------------------------------------------------------------|
| Pasteurisation (20 min, 90°C, pH 4) | Yes     | Pyrazole-3-14C-labelled penflufen and metabolite M01 (United Kingdom, 2011) |
| Baking, brewing and boiling (60 min, 100°C, pH 5) | Yes     | As above                                                                      |
| Sterilisation (20 min, 120°C, pH 6) | Yes     | As above                                                                      |
Can a general residue definition be proposed for primary crops?

| No | Primary crop metabolism not similar for all commodities (see Section 1.1.1) |

Rotational crop and primary crop metabolism similar?

| No | The metabolic profiles in wheat grain, soybean seeds and turnip roots were dominated by the pyrazole derivate metabolites M58, M63, M64, M65 resulting from the cleavage of the parent molecule at the carboxamide bond (Section 1.1.2) |

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

| Yes | Penflufen and metabolite M01 were stable under standard conditions simulating processing |

Plant residue definition for monitoring (RD-Mo)

For root and tuber and cereal crops (limited to seed and in-furrow soil treatments):
- Penflufen (sum of isomers)
- Processed commodities: not applicable
- Rotational crops: open

Plant residue definition for risk assessment (RD-RA)

For root and tuber and cereal crops (limited to seed and in-furrow soil treatments):
- Penflufen (sum of isomers)
- Processed commodities: not applicable
- Rotational crops: open

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

Matrices with high water content, high acid content and dry matrices (United Kingdom, 2011; EFSA, 2012):
- LC–MS/MS, LOQ 0.01 mg/kg for penflufen, metabolites M01 and M58 in lettuce (head), potato (tuber), dry bean (seed), carrot (leaf and root), barley (green material, grain and straw) and orange (fruit)
- Confirmatory method available for penflufen and metabolite M58
- ILV available for penflufen and metabolite M01 in potato (tuber), dry bean (seed), barley (green material, grain and straw) and orange (fruit)

EURLs (EURLs, 2018) provided for routine analyses in high water and acid content, dry and high oil content matrices following methods:
- LC–MS/MS method (QuEChERS-method EN 15662:2008) with a LOQ 0.01 mg/kg for penflufen, validated in green beans and lemons
- LC-QqQ-MS/MS QuEChERS-method with a LOQ 0.01 mg/kg for penflufen validated in wheat, barley, rice and rye
- LC–MS/MS method (QuiOil method) with a LOQ 0.01 mg/kg for penflufen, validated in cashews in a single laboratory (EFSA, 2019b).

a.i.: active ingredient; DAT: days after treatment; PBI: plant-back interval; LC–MS/MS: liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation; QuEChERS: Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method).
### B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category         | Commodity                  | T (°C) | Stability period | Compounds covered | Comment/source                                                                 |
|----------------------------------|------------------|----------------------------|--------|-----------------|--------------------|--------------------------------------------------------------------------------|
| Potato (tuber)                   | High water content | −18                        | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Lettuce (head)                   |                  | −18                        | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Wheat (forage)                   |                  | −18                        | 42     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; M01 and M03 were not detected initially (United Kingdom, 2011) |
| Soybean (forage)                 |                  | −18                        | 42     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; M01 and M03 were not detected initially (United Kingdom, 2011) |
| Turnip (leaves)                  |                  | −18                        | 41     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; penflufen, M01 and M49 were not detected initially (United Kingdom, 2011) |
| Potato (tuber)                   |                  | −18                        | 41     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; M49, M58 and M63 were not detected initially (United Kingdom, 2011) |
| Sunflower seeds                  | High oil content | −18                        | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Soybean seeds                    |                  | −18                        | 40     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; penflufen, M01, M03, M04, and M49 were not detected initially (United Kingdom, 2011) |
| Dry beans                        | High protein content | −18                      | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Wheat (grain)                    | High starch content | −18                       | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Wheat (grain)                    |                  | −18                        | 40     | Months          | Penflufen, M01, M03, M04, M49, M58, M64 | Radio-labelled samples from metabolism studies; penflufen, M01, M03, M04, and M49 were not detected initially (United Kingdom, 2011) |
| Orange (fruit)                   | High acid content | −18                        | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
| Wheat (straw)                    | Others            | −18                        | 26     | Months          | Penflufen, M01, M49, M58, M64 | Storage stability study of penflufen residues and its metabolites (United Kingdom, 2011) |
### 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) |
|-----------|------------------------|---------------------------------------------------------------|-----------------|------------------------|------------------|------------------|
| Potatoes  | NEU                    | GAP compliant trials: < 0.01; < 0.01; < 0.01; < 0.01; < 0.01;  < 0.01; < 0.01; < 0.01; < 0.01 | Trials on potato tuber (UK, 2011; Poland 2018; EFSA, 2019a) MRL\_OECD = 0.01* | 0.01* | 0.01* | 0.01* |
|           |                        | Overdosed trials (4 × 200 g a.s./ha; 2 × 250 g a.s./ha): < 0.01; < 0.01; < 0.01; < 0.01; < 0.01; < 0.01; < 0.01; < 0.01 |                 |                       |                  |                  |

GAP: Good Agricultural Practice; OECD: Organisation for Economic Co-operation and Development; 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; RA: residue levels expressed according to risk assessment 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 risk assessment (RA) refers to the whole commodity and not to the edible portion.

\[(c)\]: Supervised trials median residue. The median residue for risk assessment (RA) refers to the whole commodity and not to the edible portion.

### B.1.2.2. Residues in rotational crops

#### Overall summary

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

Inconclusive

Photolysis study of penflufen on soil is needed to adequately interpret nature of residues in confined rotational crop studies and field residue trials (data gap). The residue definition for following crops remains open. Notably, there might be residues of metabolite M01 for which a data gap on repeated dose toxicity identified during the peer review is still open.

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

Inconclusive

Data gap identified during the peer review to provide field trials on cereals, leafy vegetables, root vegetables and soybean at a dose rate covering the calculated plateau concentration of penflufen in soil to determine the residue levels of penflufen metabolites M01 (conjugated), M63 and M65 is still open (data gap).
### B.1.2.3. Processing factors

| Processed commodity | Number of valid studies | Processing factor (PF) | CF<sub>P</sub> | Comment/source |
|---------------------|-------------------------|------------------------|--------------|----------------|
|                     |                         | Individual values      | Median PF    |                |
| Not available and not required |                         |                        |              |                |

PF: Processing factor (= Residue level in processed commodity expressed according to RD-Mo/Residue level in raw commodity expressed according to RD-Mo); CF<sub>P</sub>: Conversion factor for risk assessment in processed commodity (= Residue level in processed commodity expressed according to RD-RA/Residue level in processed commodity expressed according to RD-Mo).

### B.2. Residues in livestock

| Relevance groups (subgroups) | Dietary burden expressed in mg/kg bw per day | Most critical subgroup<sup>(a)</sup> | Most critical commodity<sup>(b)</sup> | Trigger exceeded (Y/N) | Comments |
|------------------------------|--------------------------------------------|-------------------------------------|-------------------------------------|------------------------|----------|
|                              | Median | Maximum | Median | Maximum |                        |                      |
| Cattle (all)                 | 0.0015 | 0.0015  | 0.05  | 0.05    | Cattle (dairy)          | Potato, process waste | No        | –         |
| Cattle (dairy only)          | 0.0015 | 0.0015  | 0.04  | 0.04    | Cattle (dairy)          | Potato, process waste | No        | –         |
| Sheep (all)                  | 0.0016 | 0.0016  | 0.05  | 0.05    | Sheep (ram/ewe)         | Potato, process waste | No        | –         |
| Sheep (ewe only)             | 0.0016 | 0.0016  | 0.05  | 0.05    | Sheep (ram/ewe)         | Potato, process waste | No        | –         |
| Swine (all)                  | 0.0010 | 0.0010  | 0.04  | 0.04    | Swine (breeding)        | Potato, process waste | No        | –         |
| Poultry (all)                | 0.0007 | 0.0007  | 0.01  | 0.01    | Poultry (turkey)        | Potato, culls         | No        | –         |
| Poultry (layer only)         | 0.0005 | 0.0005  | 0.01  | 0.01    | Poultry (layer)         | Potato, culls         | No        | –         |
| Fish                         | –      | –       | –     | –       | –                      | –                    | –         | Not calculated |

<sup>(a)</sup>: 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’.

<sup>(b)</sup>: The most critical commodity is the major contributor identified from the maximum dietary burden expressed as ‘mg/kg bw per day’.
### B.2.1. 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/d) | Duration (days) | Comment/source                                                                 |
|------------------------------|--------------|-------------------|-----------------|-------------------------------------------------------------------------------|
| Laying hen                   | 1.94; 2.05   | 14                |                 | Laying hen, $2.8 \times 10^3$ N; [pyrazole-3-$^{14}$C] or [phenyl-UL-$^{13}$C$_6$/-$^{14}$C] labelled penflufen (United Kingdom, 2011) |
| Lactating ruminants          | 2; 2         | 5                 |                 | Lactating goat, $1.25 \times 10^3$ N; [pyrazole-3-$^{14}$C] or [phenyl-UL-$^{13}$C$_6$/-$^{14}$C] labelled penflufen (United Kingdom, 2011) |
| Fish                         | _            | _                 |                 | Not evaluated; single metabolism study with [phenyl-UL-$^{13}$C$_6$/-$^{14}$C] labelled penflufen (United Kingdom, 2011) |
Time needed to reach a plateau concentration in milk and eggs

| Animal   | Commodity | T (°C) | Stability period | Compounds covered | Comment/source |
|----------|-----------|--------|------------------|-------------------|----------------|
| Milk     | 32–72 hours | A plateau reached (after ca. 32 h for phenyl- and ca. 72 h for pyrazole-labelled penflufen) showed a diurnal pattern; no accumulation in milk after 5 daily oral administrations. |
| Eggs     | 6–8 days | The beginning of a residue plateau started approximately 6 days for pyrazole-labelled penflufen and ca. 8 days for the phenyl-label after the first administration. Low TRR levels in eggs indicates that the radioactivity did not have a tendency for accumulation |

Metabolism in rat and ruminant similar
Yes

Can a general residue definition be proposed for animals?
Yes
While the metabolism in livestock is adequately elucidated, data gaps are pending on the nature and magnitude in rotational crops (Sections 1.1.2 and 1.2.2)

Animal residue definition for monitoring (RD-Mo)
Not applicable

Animal residue definition for risk assessment (RD-RA)
Not applicable

Fat soluble residues
Yes
Log P\text{ow} of penflufen is 3.3

Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs)
Not applicable and not available during the peer review. During this review, the EURLs provided a LC–MS/MS method (EN 15662:2008 (QuEChERS method)) for routine analyses of penflufen, LOQ = 0.01 mg/kg; supported by validation data in swine meat and liver and whole cow milk (EURLs, 2018)

B.1.2.2. Stability of residues in livestock

| Animal products (available studies) | Animal | Commodity | T (°C) | Stability period Value | Unit | Compounds covered | Comment/source |
|-------------------------------------|--------|-----------|--------|------------------------|------|-------------------|----------------|
| Studies not available and not required |        |           |        |                        |      |                   |                |
B.2.2. Magnitude of residues in livestock

B.2.2.1. Summary of the residue data from livestock feeding studies

| Animal commodity     | Residues at the closest feeding level (mg/kg) | Estimated value at 1N | MRL proposal (mg/kg) | CF<sup>(c)</sup> |
|----------------------|-----------------------------------------------|----------------------|---------------------|-----------------|
|                      | Mean Highest STMR<sub>Mo</sub><sup>(a)</sup> (mg/kg) | HR<sub>Mo</sub><sup>(b)</sup> (mg/kg) |                     |                 |
| Cattle (all)         | – no studies are available and not required   |                      |                     |                 |
| Cattle (dairy only)  | – no studies are available and not required   |                      |                     |                 |
| Sheep (all)          | – no studies are available and not required   |                      |                     |                 |
| Sheep (ewe only)     | – no studies are available and not required   |                      |                     |                 |
| Swine (all)          | – no studies are available and not required   |                      |                     |                 |
| Poultry (all)        | – no studies are available and not required   |                      |                     |                 |
| Poultry (layer only) | – no studies are available and not required   |                      |                     |                 |

(a): Median residues expressed according to the residue definition for monitoring, recalculated at the 1N rate for the median dietary burden.
(b): Highest residues expressed according to the residue definition for monitoring, recalculated at the 1N rate for the maximum dietary burden.
(c): Conversion factor to recalculate residues according to the residue definition for monitoring to the residue definition for risk assessment.

B.3. Consumer risk assessment

B.3.1. Consumer risk assessment without consideration of the existing CXLs

ARfD

Highest IESTI, according to EFSA PRIMo (rev.2.3)

NESTI (% ARfD)

Assumptions made for the calculations

|                        | 0.5 mg/kg bw (EFSA, 2012) |
|------------------------|---------------------------|
| Potatoes:              | 0.3% of ARfD              |
| NESTI (% ARfD)         | Not assessed in this review |

The calculation is based on the highest residue levels expected in raw agricultural commodities. The contributions of commodities where no GAP on penflufen was reported in the framework of the MRL review were not included in the calculation (see Section 3).

ARfD: acute reference dose; bw: body weight; NESTI: national estimated short-term intake; PRIMo: (EFSA) Pesticide Residues Intake Model; WHO: World Health Organization; IESTI: international estimated short-term intake; GAP: Good Agricultural Practice; MRL: maximum residue level.
Consumer exposure assessment through drinking water resulting from groundwater metabolite(s) according to SANCO/221/2000 rev.10 Final (25/02/2003)

| Metabolite(s) | ADI (mg/kg bw per day) | Intake of groundwater metabolites (% ADI) |
|---------------|------------------------|------------------------------------------|
|               |                        |                                          | Not assessed in this review |

Proposed MRLs

| Code number | Commodity                  | Existing EU MRL (mg/kg) | Existing CXL (mg/kg) | Outcome of the review |
|-------------|-----------------------------|-------------------------|----------------------|-----------------------|
| 0211000     | Potatoes                    | 0.01*                   | –                    | 0.01* Recommended(a)  |
| –           | Other commodities of plant and/or animal origin | See Art 18(1)(b) Reg 396/2005 | –                    | –                     | 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 H-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)**

#### Penflufen

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

| Toxicological end points | ADI (mg/kg bw per day) | ARfD (mg/kg bw) |
|--------------------------|------------------------|-----------------|
|                          | 0.04                   | 0.5             |

| Source of ADI                  | EFSA                  | Source of ARfD  |
|--------------------------------|-----------------------|-----------------|
| Year of evaluation             | 2012                  | Year of evaluation | 2012 |

| No of diets exceeding ADI | 0.1 NL child | 0.1 PT General population | 0.1 FR toddler | 0.1 SE general population 90th percentile | 0.1 FR infant | 0.1 WHO cluster diet D | 0.1 WHO regional European diet | 0.1 WHO cluster diet E | 0.1 UK Toddler | 0.1 FR all population | 0.1 DE child | 0.1 DK child | 0.1 IE adult | 0.0 ES child | 0.0 DK adult | 0.0 UK Adult | 0.0 UK vegetarian | 0.0 FR all population | 0.0 ES adult | 0.0 IT kids/toddler | 0.0 IT adult |
|---------------------------|---------------|----------------------|----------------|-------------------------------------------|--------------|-----------------------|------------------------|---------------------------|----------------|---------------------|----------------|---------------|----------------|----------------|----------------|----------------|-------------------|-------------------|----------------|----------------|----------------|----------------|
| Commodity/group of commodities | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) |

#### Chronic risk assessment

| MS Diet | 2nd contributor to ADI | 3rd contributor to ADI | pTMRLs at LOQ (in % of ADI) |
|---------|------------------------|------------------------|-----------------------------|
|         | Commodity/group of commodities | Commodity/group of commodities |                               |
|         | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | FRUIT (FRESH OR FROZEN) | Potatoes | 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 Penflufen is unlikely to present a public health concern.
# Acute risk assessment/children

| Highest % of ARfD/ADI | Commodities | pTMRL/Threshold MRL (mg/kg) |
|-----------------------|-------------|----------------------------|
| 0.0                   | Potatoes    | 0.01/-                     |
| 0.0                   | Fried potatoes | 0.01/-                   |

# Acute risk assessment/adults/general population

| Highest % of ARfD/ADI | Commodities | pTMRL/Threshold MRL (mg/kg) |
|-----------------------|-------------|----------------------------|
| 0.0                   | Potatoes    | 0.01/-                     |
| 0.0                   | Fried potatoes | 0.01/-                   |

---

- 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.

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- There was no exceedance of the ARfD/ADI for any unprocessed commodity.
- For Penflufen, IESTI 1 and IESTI 2 were calculated for food commodities for which pTMRLs were submitted and for which consumption data are available.
- 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.

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

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- Conclusion:
  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                |
| Potato, culls                | 0.01*                 | STMR                   | 0.01*                 | HR                     |
| Potato, process waste        | 0.01*                 | STMR(α)                | 0.01*                 | STMR(α)                |
| Potato, dried pulp           | 0.01*                 | STMR(α)                | 0.01*                 | STMR(α)                |

Risk assessment residue definition: Penflufen (sum of isomers)

STMR: supervised trials median residue; HR: highest residue; PF: processing factor.
*: Indicates that the input value is proposed at the limit of quantification.
(α): For potato, process waste and potato dried pulp, no default processing factor was applied because penflufen is applied early in the growing season and residues are expected to be below the LOQ. 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               |
| Potatoes          | 0.01*                   | STMR                  | 0.01*                   | HR                    |

*: Indicates that the input value is proposed at the limit of quantification.
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 DM in EU?
  - Yes
  - MRL And RA derived in Section 3?
    - Yes
    - MRL fully supported by data?
      - Yes
      - GAP or DB > 0.1 mg/kg DM in EU?
        - Yes
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - No
          - MRL fully supported by data?
            - Yes
            - MRL is recommended.
            - Comparison with CXLs
          - No
          - Specific LOQ or default MRL?
            - Yes
            - MRL is recommended.
            - Comparison with CXLs
          - No
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
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          - MRL is recommended.
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          - MRL is recommended.
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          - Comparison with CXLs
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          - MRL is recommended.
          - Comparison with CXLs
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          - MRL is recommended.
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
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          - MRL is recommended.
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          - MRL is recommended.
          - Comparison with CXLs
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          - MRL is recommended.
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
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        - Specific LOQ or default MRL?
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          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
          - Yes
          - MRL is recommended.
          - Comparison with CXLs
        - No
        - Specific LOQ or default MRL?
Review of the existing MRLs for penflufen

Comparison of the EU recommendation with the existing CXL

- CXL available?:
  - Yes
    - RD comparable?:
      - Yes
        - CXL higher?:
          - Yes
        - No
      - No
    - No
- No

Consumer risk assessment with consideration of the existing CXL

- CXL supported by data?:
  - Yes
    - Risk identified?:
      - Yes
        - Codex median/ highest residues are included in the RA.
      - No
    - No
  - No

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(a) | IUPAC name/SMILES notation/InChiKey(b) | Structural formula(c) |
|----------------------|----------------------------------------|-----------------------|
| penflufen            | 5-fluoro-1,3-dimethyl-N-[2-((2RS)-4-methylpentan-2-yl)phenyl]-1H-pyrazole-4-carboxamide | ![Structural formula](image1) |
|                      | O-C(Nc1ccccc1C(C(C)(C)c1c(F)n(C)nc1C |                     |
|                      | GOFJDXXZHFNFV-UHFFFAOYSA-N           |                      |
| penflufen-3-hydroxybutyl (M01) | 5-fluoro-N-[2-[(2RS)-4-hydroxy-4-methylpentan-2-yl]phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide | ![Structural formula](image2) |
|                      | O-C(Nc1ccccc1C(C)(C)c1c(F)n(C)nc1C |                     |
|                      | SBLHNSPRVRRR-J-UHFFFAOYSA-N         |                      |
| penflufen-3-hydroxybutyl-glucoside (M03) | 5-fluoro-N-[4-((β-D-glucopyranosyloxy)-4-methylpentan-2-yl]phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide | ![Structural formula](image3) |
|                      | Fc1n(C)c1C=O]nc1ccccc1C(C)(C)c1c(F)n(C)nc1C |                     |
|                      | JULDOKNYPCMRL-QIFIURJSA-N           |                      |
| penflufen-3-hydroxybutyl-malonyl-glucoside (M04) | 4-([5-fluoro-1,3-dimethyl-1H-pyrazole-4-carbonyl]amino)phenyl]-2-methylpentan-2-yl 6-O-(carboxyacetyl)-β-D-glucopyranoside | ![Structural formula](image4) |
|                      | Fc1n(C)c1C=O]nc1ccccc1C(C)(C)c1c(F)n(C)nc1C |                     |
|                      | GLRAVPSKCYDCW-RLFCDCOUSA-N          |                      |
| penflufen-4-hydroxybutyl-malonyl-glucoside (M05) | 4-([5-fluoro-1,3-dimethyl-1H-pyrazole-4-carbonyl]amino)phenyl]-2-methylpentyl 6-O-(carboxyacetyl)-β-D-glucopyranoside | ![Structural formula](image5) |
|                      | Fc1n(C)c1C=O]nc1ccccc1C(C)(C)c1c(F)n(C)nc1C |                     |
|                      | IEMNTFGXHROXY-RPODPBEFSA-N          |                      |
| penflufen-glutathione (M48) | γ-glutamyl-S-(1,3-dimethyl-4-[2-(4-methylpentan-2-yl)phenyl]carbamoyl]-1H-pyrazol-5-yl)cysteinylglycine | ![Structural formula](image6) |
|                      | O-C(Nc1ccccc1C(C)(C)c1c(SCC(N=O)CCC(N=O)O)(C=O)NCC(=O)n(C)nc1C |                     |
|                      | RSIFLCQCEINIDU-UHFFFAOYSA-N         |                      |
| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation/InChiKey<sup>(b)</sup> | Structural formula<sup>(c)</sup> |
|-------------------------------|-------------------------------------------------|---------------------------------|
| penflufen-homoglutathione (M49) | γ-glutamyl-S-[1,3-dimethyl-4-[(2R5)-4-methylpentan-2-yl]phenyl] carbamoyl]-1H-pyrazol-5-yl]cysteinyl-β-alanine | ![Structural formula](image) |
| | O=C(Nc1cccc1C(CC(C(C)c2c(SCC(NC(=O)CCC(NC(=O)O))(-O)NCC(-O)O)n(C)nc2C | KEKGDOAKVJULQ-UHFFFAOYSA-N |
| penflufen-cystein (M53) | S-[1,3-dimethyl-4-[(4-methylpentan-2-yl)phenyl] carbamoyl]-1H-pyrazol-5-yl)cysteinyl | ![Structural formula](image) |
| | O=C(Nc1cccc1C(CC(C(C)c1c(SCC(NC(=O)O)n(C)nc1C) | SSIKTHIOKDEJG-UHFFFAOYSA-N |
| Penflufen-pyrazole-4-carboxamide (M58) | 5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide | ![Structural formula](image) |
| | O=C(N)c1c(F)n(C)nc1C | IOGCHBMFOXWVL-YHFFFAOYSA-N |
| penflufen-desmethyl-dicarboxylic acid (M63) | 5-fluoro-1H-pyrazole-3,4-dicarboxylic acid | ![Structural formula](image) |
| | OC(=O)c1c([NH]nc1F)C(=O)O | QSHD MBAFV0QGT-UHFFFAOYSA-N |
| penflufen-bis-desmethyl-3-carboxylic acid (M64) | 3-fluoro-1H-pyrazole-5-carboxylic acid | ![Structural formula](image) |
| | O=C(O)c1cc(F)n[NH]1 | LSQNHKORGLHIMY-UHFFFAOYSA-N |
| penflufen-bis-desmethyl-3-carbonyl serine (M65) | structure not completely specified, one possible isomer is shown | ![Structural formula](image) |
| | N-(5-fluoro-1H-pyrazole-3-carbonyl)serine | QIKUTFALRZFUFV-UHFFFAOYSA-N |

SMILES: simplified molecular-input line-entry system.

<sup>(a)</sup> The metabolite name in bold is the name used in the conclusion.

<sup>(b)</sup> ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 Dec 2014).

<sup>(c)</sup> ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 Dec 2014).