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

European Food Safety Authority (EFSA),
Alba Brancato, Daniela Brocca, Luis Carrasco Cabrera, Chloe De Lentdecker, Zoltan Erdos, Lucien Ferreira, Luna Greco, Samira Jarrah, Dimitra Kardassi, Renata Leuschner, Alfonso Lostia, Christopher Lythgo, Paula Medina, Ileana Miron, Tunde Molnar, Ragnor Pedersen, Hermine Reich, Angela Sacchi, Miguel Santos, Alois Stanek, Juergen Sturma, Jose Tarazona, Anne Theobald, Benedicte Vagenende and Laura Villamar-Bouza

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 sintofen. To assess the occurrence of sintofen residues in plants, processed commodities, rotational crops and livestock, EFSA considered the conclusions derived in the framework of Commission Regulation (EC) No 33/2008, as well as the European authorisations reported by Member States (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 derived by EFSA still requires further consideration by risk managers.

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Keywords: sintofen, MRL review, Regulation (EC) No 396/2005, consumer risk assessment, plant growth regulator

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Correspondence: pesticides.mrl@efsa.europa.eu
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Summary

Sintofen was included in Annex I to Directive 91/414/EEC on 1 June 2011 by Commission Implementing Directive 2011/40/EU, and has been deemed to be approved under Regulation (EC) No 1107/2009, in accordance with Commission Implementing Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011. As the active substance was approved after the entry into force of Regulation (EC) No 396/2005 on 2 September 2008, the European Food Safety Authority (EFSA) is required to provide a reasoned opinion on the review of the existing maximum residue levels (MRLs) for that active substance in compliance with Article 12(1) of the aforementioned regulation.

As the basis for the MRL review, on 16 August 2017, EFSA initiated the collection of data for this active substance. In a first step, Member States were invited to submit their national Good Agricultural Practices (GAPs) by 15 September 2017, in a standardised way, in the format of specific GAP forms allowing the rapporteur Member State (RMS), France, 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 8 December 2017. On the basis of all the data submitted by Member States, EFSA asked France, the designated RMS, to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report. The PROFile and evaluation report, together with Pesticide Residues Intake Model (PRIMo) calculations were provided by the RMS to EFSA on 12 February 2018. Following a completeness check undertaken by EFSA, a request for further clarifications was addressed to the RMS on 22 March 2018. After having considered all the information provided, EFSA finalised the completeness check report which was made available to Member States on 28 May 2018.

Based on the information provided by the RMS and Member States and taking into account the conclusions derived by EFSA in the framework of Commission Regulation (EC) No 33/2008, EFSA prepared in May 2018 a draft reasoned opinion, which was circulated to Member States for consultation via a written procedure. Comments received by 18 June 2018 were considered during the finalisation of this reasoned opinion.

The following conclusions are derived.

The metabolism of sintofen was investigated in cereals (wheat) after foliar treatment. A residue definition for risk assessment for cereal grain is proposed as follows: sum of sintofen (free and sugar conjugates) and SC 3095 (free and sugar conjugates), expressed as sintofen. The same residue definition for risk assessment is proposed on a tentative basis for cereal straw. A residue definition for enforcement is proposed as sintofen. A validated analytical method with a limit of quantification (LOQ) of 0.01 mg/kg in wheat grain and with a LOQ of 0.05 mg/kg in wheat straw is available. Storage stability data of sintofen and metabolite SC 3095 are available for wheat grain and wheat straw.

The data on metabolism and distribution of sintofen in rotational crops indicated that the metabolism in rotational crops is similar to the pathway observed in primary crops. Studies investigating the stability of sintofen to hydrolysis under standard conditions of pasteurisation, baking/brewing/boiling and sterilisation were not available for this review. Nevertheless, they are not necessary since residues in raw commodities were below the LOQ and the chronic exposure is below 10% of the acceptable daily intake (ADI). Studies investigating the magnitude of residues in processed commodities are not required.

The available data are considered sufficient to derive tentative MRL proposals as well as risk assessment values for wheat grain and wheat straw. It is noted that MRLs were not derived to consider the potential residue uptakes in rotational crops as it is assumed that residues from rotational crops can be avoided. A mitigation measure such as ‘crop not to be rotated with a PBI shorter than 365 days’ was tentatively proposed.

Studies investigating the metabolism in livestock were conducted on lactating goats. 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.

Chronic 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 WHO cluster diet B, representing 0.1% of the ADI.

Based on these calculations, EFSA concludes that the use of sintofen results in a consumer exposure lower than the toxicological reference value. Therefore, this use is unlikely to pose a risk to consumer’s health, noting that there is still uncertainty linked to the major data gaps (residue levels of metabolite SC 1231 in cereal straw). Acute exposure calculations were not carried out because an acute reference dose (ARFD) was not deemed necessary for this active substance.
Background

Regulation (EC) No 396/2005¹ (hereinafter referred to as ‘the Regulation’) establishes the rules governing the setting and the review of pesticide maximum residue levels (MRLs) at European level. Article 12(1) of that Regulation stipulates that the European Food Safety Authority (EFSA) shall provide within 12 months from the date of the inclusion or non-inclusion of an active substance in Annex I to Directive 91/414/EEC² a reasoned opinion on the review of the existing MRLs for that active substance. As sintofen was included in Annex I to Council Directive 91/414/EEC on 1 June 2011 by means of Commission Implementing Directive 2011/40/EU³, and has been deemed to be approved under Regulation (EC) No 1107/2009⁴, in accordance with Commission Implementing Regulation (EU) No 540/2011⁵, as amended by Commission Implementing Regulation (EU) No 541/2011⁶, EFSA initiated the review of all existing MRLs for that active substance.

According to the legal provisions, EFSA shall base its reasoned opinion in particular on the relevant assessment report prepared under Directive 91/414/EEC 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 Directive 91/414/EEC is therefore insufficient for the assessment of all existing MRLs for a given active substance.

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

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

As the basis for the MRL review, on 16 August 2017 EFSA initiated the collection of data for this active substance. In a first step, Member States were invited to submit by 15 September 2017 their national Good Agricultural Practices (GAPs) authorised in Member States, in a standardised way, in the format of specific GAP forms. Based on the GAP data submitted, the rapporteur Member State (RMS) France 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, Member States were requested to provide residue data supporting the critical GAPs by 8 December 2017.

On the basis of all the data submitted by Member States and the EU Reference Laboratories for Pesticides residues (EURL), EFSA asked France, the designated RMS in the framework of Commission Regulation (EC) No 33/2008, to complete the PROFile and to prepare a supporting evaluation report. The PROFile and the supporting evaluation report, together with the Pesticide Residues Intake Model (PRIMo) calculations, were submitted to EFSA on 12 February 2018. Following a completeness check undertaken by EFSA, a request for further clarifications was addressed to the RMS on 22 March 2018. After having considered all the information provided, EFSA finalised the completeness check report which was made available to all Member States on 28 May 2018.

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¹ Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.
² Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32. Repealed by Regulation (EC) No 1107/2009.
³ Commission Implementing Directive 2011/40/EU of 11 April 2011 amending Council Directive 91/414/EEC to include sintofen as active substance and amending Commission Decision 2008/934/EC. OJ L 97, 12.4.2011, p. 34–37.
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.
Based on the information provided by the RMS, Member States and the EURL, and taking into account the conclusions derived by EFSA the framework of Commission Regulation (EC) No 33/2008, EFSA prepared in May 2018 a draft reasoned opinion, which was circulated to Member States for commenting via a written procedure. All comments received by 18 June 2018 were considered by EFSA during the finalisation of the reasoned opinion.

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

In addition, further supporting documents to this reasoned opinion are the completeness check report (EFSA, 2018a) and the Member States consultation report (EFSA, 2018b). These reports are developed to address all issues raised in the course of the review, from the initial completeness check to the reasoned opinion. Furthermore, the exposure calculations for the 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

Sintofen is the ISO common name for 1-(4-chlorophenyl)-1,4-dihydro-5-(2-methoxyethoxy)-4-oxocinnoline-3-carboxylic acid (IUPAC).

The chemical structure of the active substance and its main metabolites are reported in Appendix F.

Sintofen was evaluated following re-submission application according to Commission Regulation (EC) No 33/2008 with France designated as RMS. The representative use evaluated was outdoor foliar spraying as a plant growth regulator for plant breeding purposes in wheat. Following the peer review, which was carried out by EFSA, a decision on inclusion of the active substance in Annex I to Directive 91/414/EEC was published by means of Commission Implementing Directive 2011/40/EU, which entered into force on 1 June 2011. According to Regulation (EU) No 540/2011, as amended by Commission Implementing Regulation (EU) No 541/2011, sintofen is deemed to have been approved under Regulation (EC) No 1107/2009. This approval is restricted to uses as a plant growth regulator on wheat for hybrid seed production not intended for human consumption. Furthermore, confirmatory information was requested, among others, as regards the metabolic profile of sintofen in rotational crops, to be submitted by 31 May 2013. The review report was revised (European Commission, 2014) to consider the assessment that has been carried out in line with the Guidance document on the procedures for submission and assessment of confirmatory data following inclusion of an active substance in Annex to Regulation (EC) No 541/2011 (European Commission, 2013).

For sintofen 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 sintofen are not available. MRL changes have not occurred since the entry into force of the Regulation mentioned above.

For the purpose of this MRL review, all the uses of sintofen currently authorised within the EU have been notified by Member States during the GAP collection and reported by the RMS in the GAP overview file. The critical GAPs identified in the overview file were then summarised in the PROFile and considered in the assessment. The details of the authorised critical uses (GAPs) for sintofen 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 PROFile submitted by the RMS, the draft assessment report (DAR) prepared under Council Directive 91/414/EEC (France, 2007), the additional report and its addenda prepared under Commission Regulation (EC) No 33/2008 (France, 2010a,b), the review report on sintofen following the confirmatory data assessment (European Commission, 2014) and the conclusion on the peer review of the pesticide risk assessment of the active substance sintofen (EFSA, 2010). The EURL evaluation report on analytical methods (EURL, 2018) was also considered in the assessment.

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, 2017; OECD, 2011, 2013).

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

1. Residues in plants

1.1. Nature of residues and methods of analysis in plants

1.1.1. Nature of residues in primary crops

Three metabolism studies of sintofen on wheat were reported (France, 2010b, 2018), with the first two studies assessed in the framework of the peer review (EFSA, 2010).

In the first study, sintofen was labelled on the chlorophenyl ring only. After foliar applications at a weekly interval of 150 μg a.s./plant (equivalent to 3,000 g a.s./ha), in immature plants (preharvest interval (PHI): 14 days) the major constituents of the residue were the unchanged parent compound (59% of total radioactive residue (TRR)), the desmethyl sintofen SC 3095 and its glucose conjugate, occurring, respectively, at 13% and 27% of TRR before enzymatic hydrolysis step. After hydrolysis, the level of parent sintofen remained unchanged while the residue level of SC 3095 increased up to 40% of TRR while no glucose conjugate of SC 3095 was recovered (EFSA, 2010). A further study after a foliar application of 1,500 g a.s./ha at BBCH 31, where wheat was harvested at maturity (PHI: 100 days), sintofen and its metabolite SC 3095 were present in straw (14% and 9.6% of TRR, respectively) along with very minor metabolites (<0.01 mg/kg) not further characterised. In contrast, neither the parent nor the metabolite SC 3095 was detected in grain where only one metabolite was found at a significant level (34.2% of TRR; 0.013 mg/kg) without any further identification (EFSA, 2010).

In the peer review, it was noted that the absence of sintofen and SC 3095 in mature wheat grain was not confirmed in the supervised residue trials performed at dose rates of 1,200–1,465 g a.s./ha where the residues of sintofen and metabolite SC 3095 were found up to 0.061 and 0.05 mg/kg, respectively, in the F1 grain (EFSA, 2010). However, since the analytical method used to generate the residue trials included an enzymatic hydrolysis step, it was not possible to distinguish between free and conjugated forms of the metabolite SC 3095 and whether the parent compound was effectively present either as a free or as a conjugated form. However, it was not expected that sintofen conjugates residues contribute significantly to the residue levels determined in the residue trials due to its chemical structure.

A third metabolism study was performed with sintofen labelled on the chlorophenyl and cinnoline (phenyl) rings (France, 2018). After one foliar application of ca 1,200–1,400 g a.s./ha at growth stage BBCH 32–37, the major constituents of the residue in the wheat grain were sintofen (21–40% TRR; 0.029–0.059 mg eq/kg) and metabolite SC 3095 present in both free (5.1–6.2% TRR; 0.007–0.008 mg eq/kg) and conjugated form (5.6–13.1% TRR; 0.008–0.018 mg eq/kg), while metabolite SC 1231 was present at very low levels (1.2–1.3% TRR; 0.002 mg eq/kg). In wheat straw, sintofen was detected at 72.4–75.5% of TRR (28.9–29.4 mg eq/kg), SC 3095 at 1.8–3.9% TRR (0.70–1.52 mg eq/kg) and SC 1231 at 2.8–3.0% TRR (1.09–1.17 mg eq/kg). In this second study, a new metabolite SC 1231 was identified at relevant levels in wheat straw.

Both studies were sufficient to understand the metabolic pathway of sintofen in wheat.

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

Sintofen is authorised on wheat that may be grown in rotation. The field DT$_{90}$ reported in the soil dissipation studies evaluated in the framework of the peer review was more than 1 year (EFSA, 2010). One confined rotational crop study was assessed in the framework of the peer review (EFSA, 2010). However, the metabolism of sintofen in rotational crops was considered not fully addressed and a data gap was set for a new rotational crop metabolism study (EFSA, 2010).

To address this data gap, a new confined rotational crop study was evaluated as part of the confirmatory data process (France, 2018). Sintofen, labelled on the chlorophenyl and cinnoline(phenyl) rings, was applied onto bare soil at a nominal concentration of 1.15 mg a.s./kg soil. This concentration corresponds to the accumulation plateau which is reached after 10–12 years, i.e. it is the predicted maximum concentration in soil after 10 years of a single application of sintofen every 2 years without considering ploughing. It is noted that soil metabolites have not been identified due to the persistence of the active substance (EFSA, 2010), and therefore, there is no soil predicted environmental concentration (PEC) for metabolite SC 3095. Since the rotational crop study was dosed at a level above the accumulated soil estimate for parent sintofen, it is considered that the study provided the needed evidence for metabolite SC3095 and conjugates. Lettuce, radish and wheat were planted at plant-back intervals (PBI) of 30, 90/104 and 368 days after soil treatment (DAT). In radish, the only significant residue levels were of sintofen 30 DAT in radish roots (0.012–0.014 mg eq/kg) and 90 DAT in radish foliage (0.019–0.025 mg eq/kg). In immature lettuce, the only residue present at relevant levels was sintofen 30 DAT (0.011 mg eq/kg). In radish and lettuce, all residues were below 0.01 mg/kg 368 DAT. In wheat grain, the only significant residues were SC 3095 conjugates, detected at 0.020 mg eq/kg 30 DAT, decreasing to 0.010 mg eq/kg 368 DAT. In wheat straw, relevant residues were sintofen (0.022–0.034 mg eq/kg), SC 3095 free (0.010–0.018 mg eq/kg) and conjugated (0.019–0.029 mg eq/kg) 30 DAT. At 368 DAT, only SC 3095 was observed at significant levels (0.022–0.024 mg eq/kg) in wheat straw. The metabolites identified in rotational crops suggested that the metabolism is similar to that in primary crops.

1.1.3. Nature of residues in processed commodities

There were no studies investigating the nature of residues of sintofen in processed commodities available for this review. For all raw commodities, residues were below 0.1 mg/kg and the chronic exposure is below 10% of the acceptable daily intake (ADI). Therefore, the investigation of the nature of residues in processed commodities is not required.

1.1.4. Methods of analysis in plants

An analytical method using liquid chromatography with tandem mass spectrometry (LC–MS/MS) was validated for the determination of sintofen in wheat grain (dry matrix) with a limit of quantification (LOQ) of 0.01 mg/kg and in wheat straw with a LOQ of 0.05 mg/kg (EFSA, 2010). Furthermore, the EURL reported a method using LC–MS/MS for high water, high acid, high oil content and dry matrices with a LOQ of 0.01 mg/kg (EURL, 2018).

Hence, it can be concluded that sintofen can be enforced in wheat grain with a LOQ of 0.01 mg/kg and in wheat straw with a LOQ of 0.05 mg/kg.

1.1.5. Stability of residues in plants

In the framework of the peer review, the storage stability of sintofen and its metabolite SC 3095 was separately demonstrated in dry/starch (wheat grain) and wheat straw for –20°C for at least 18 months (EFSA, 2010).

1.1.6. Proposed residue definitions

The metabolism of sintofen was investigated on wheat (the only authorised use). It must be highlighted that a conclusion on the nature of residues in primary crops is derived from the metabolic pathway depicted in both studies in the F1 grain generation and extrapolated to the F2 wheat grain generation. This was considered acceptable as the overdosing needed to provide sufficient total residue levels to be characterised in the F2 grains, is likely to cause phytotoxicity. Moreover, the significant growth dilution rate expected from F1 generation seeds to F2 grains justifies that the F1 seeds metabolism studies can be relied upon (EFSA, 2010). Metabolite SC 3095 is the main metabolite
of sintofen found in rats and therefore the reference values of the parent are applicable to this metabolite as well (EFSA, 2010).

Consequently, the residue definition for risk assessment in cereal grain can be proposed as follows: sum of sintofen (free and sugar conjugates) and SC 3095 (free and sugar conjugates), expressed as sintofen. The same residue definition for risk assessment is proposed for cereal straw. However, this proposal is tentative for straw since the absence of metabolite SC 1231 in F2 cereal straw generation was not fully demonstrated. It is noted that the RMS proposed a waiver on this matter (France, 2018). However, additional residue trials confirming this assumption are still required (data gap).

For enforcement, the residue definition is proposed as sintofen for cereal grain and straw, as parent alone is a sufficient marker in these matrices (EFSA, 2010). A validated method for the proposed residue definition for enforcement in wheat grain at the LOQ of 0.01 mg/kg and in wheat straw at the LOQ of 0.05 is available (EFSA, 2010). In addition, a validated method in the four main plant matrices is available (EURL, 2018).

1.2. Magnitude of residues in plants

1.2.1. Magnitude of residues in primary crops

To assess the magnitude of sintofen residues resulting from the reported GAPs, EFSA considered all residue trials reported by the RMS in its evaluation report (France, 2018) and evaluated in the framework of the peer review (EFSA, 2010). All residue trial samples considered in this framework were stored in compliance with the conditions for which residues were demonstrated to be stable. Decline of residues during storage of the trial samples is therefore not expected.

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

The available residue trials are sufficient to derive MRL and risk assessment values for wheat, taking note of the following considerations:

- Wheat: the number of residue trials supporting the southern/northern outdoor GAPs is not compliant with the data requirements for this crop. However, the reduced number of residue trials is considered acceptable in these cases because all results were below the LOQ and a no-residue situation is expected. Further residue trials are therefore not required.

Considering that different residue definitions are proposed for enforcement and risk assessment, a conversion factor would need to be considered. However, since residue trials that were simultaneously analysed according to the residue definition for enforcement and risk assessment showed no residues of both parent and metabolite SC 3095, a conversion factor of 1 is proposed.

1.2.2. Magnitude of residues in rotational crops

A cold rotational crop field trial was assessed in the framework of the peer review (EFSA, 2010). However, in the framework of the peer review, it was considered that the study was not performed at the appropriate dose rate of application to cover the accumulation of sintofen residues in soil. As a consequence, a data gap was set to provide cold rotational crop field trials at the appropriate dose rate of application covering the predicted maximum concentration of sintofen in soil. No cold rotational crop field trial studies were available for this review; however, the new confined rotational crop study was performed with an appropriate dose rate of application to cover the accumulation of sintofen residues in soil and deemed sufficient to address the impact of residues in rotational crops.

The confined rotational crop study confirmed the occurrence of residues at relevant levels in crops that can be rotated up to 365 DAT (see Section 1.1.2 for further details). Based on the available data, there are indications that applying mitigation measures would allow limiting the residue uptake to levels below the LOQ in all crops that can be grown in rotation. One possible mitigation measure could be ‘crop not to be rotated with a PBI shorter than 365 days’. However, it highlighted that this remains an indicative assessment based on the confined rotational crop studies. In order to confirm or refine this proposed mitigation measure, field rotational crop studies covering the plateau level may still be requested at national level.

It should be noted that in its evaluation report, the RMS was of the opinion that residue levels were not expected to exceed the LOQ in rotational crops (France, 2018). Among the argumentation presented was that sintofen is an active substance which is restricted to uses only in winter wheat as a
hybridising agent; the product is not applied over the entire surface of the plot but in strip to approximately 50% of the crop; the scenario of repeated application every 2 years on the same plot for 10 consecutive years is not likely to occur; the soil concentration of 1.15 mg/kg is a worst case as ploughing is not considered (France, 2018). As a consequence, the RMS considered that no specific mitigation measure should be needed for rotational crops.

Although EFSA considers that a mitigation measure may need to be considered, it is noted that any decision on the implementation of mitigation measures is usually dealt with at national level by Member States. In this context, additional rotational crop field trials might be provided.

1.2.3. Magnitude of residues in processed commodities

For all raw commodities, residues were below 0.1 mg/kg and the chronic exposure is below 10% of the ADI. Therefore, the investigation of the nature of residues in processed commodities is not required.

Further processing studies are not required as they are not expected to affect the outcome of the risk assessment. However, if processing factors were to be required by risk managers, in particular for enforcement purposes, additional processing studies would be needed.

1.2.4. Proposed MRLs

The available data are considered sufficient to derive tentative MRL proposals as well as risk assessment values for wheat grain. It is noted that MRLs were not derived to consider the potential residue uptakes in rotational crops as it is assumed that residues from rotational crops can be avoided. A mitigation measure such as ‘crop not to be rotated with a PBI shorter than 365 days’ is tentatively proposed. Tentative MRLs were also derived for wheat straw in view of the future need to set MRLs in feed items.

2. Residues in livestock

Sintofen is authorised for use on wheat 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. It should be noted that the calculation did not considered residues from rotational crops since it was assumed that mitigation measures can be implemented to avoid any residue uptakes in rotational crops (see Section 1.2.2). 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.

Although not required, one study investigating the metabolism of sintofen in livestock was conducted on lactating goats (France, 2010b) and assessed in the framework of the peer review (EFSA, 2010). Lactating goats were dosed twice a day with an oral administration of [14C]-sintofen in gelatine capsules over a period of seven consecutive days. Two dose rates were tested (0.01 mg/kg body weight (bw) per day (low-dose level) and 1.23 mg/kg bw per day (high-dose level)), covering the maximum dietary burdens calculated for all ruminants. Sintofen was detected respectively in liver and kidney at 0.018 mg/kg and 0.071 mg/kg, respectively, only in the high-dose level. In other tissues and milk, TRR were very low (< 0.01 mg eq/kg) in both dose levels. No metabolite fractions were detected at relevant levels in any tissues.

In the framework of the peer review, a residue definition for risk assessment and enforcement was proposed as sintofen only (EFSA, 2010). For this MRL review, no residue definition for livestock is necessary.

If future uses would lead to the need to set a residue definition for livestock and based on the results of the metabolism study assessed above, the residue definition for enforcement and risk assessment proposed in the framework of the peer review is applicable.

No feeding studies were available or required for this MRL review. In addition, no validated analytical methods for animal matrices were reported or required.

3. Consumer risk assessment

Chronic exposure calculations for the 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 wheat grain where a tentative 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. Acute exposure calculations were not carried out because an acute reference dose (ARfD) was not deemed necessary for this active substance.

The calculation was based on the median residue levels in wheat grain. The calculation does not consider residues in rotational crops as it is assumed that mitigation measures would be sufficient and implemented to avoid any residue uptake in rotational crop (see Section 1.2.2). The contributions of commodities where no GAP was reported in the framework of this review were not included. The exposure values calculated were compared with the toxicological reference value for sintofen, derived by EFSA (2010). The highest chronic exposure was calculated for WHO cluster diet B, representing 0.1% of the ADI.

It is noted that considering the MRLs from the confined rotational crop study (Section 1.1.2) in the consumer exposure would not affect significantly the outcome of the risk assessment. Indicative calculations performed by EFSA confirmed the assessment of the RMS, with the highest chronic exposure representing less than 2% of the ADI (see also France, 2018).

Based on these calculations, EFSA concludes that the use of sintofen results in a consumer exposure lower than the toxicological reference value. Therefore, this use is unlikely to pose a risk to consumer's health, noting that there is still uncertainty linked to the major data gap (residue levels of metabolite SC 1231 in cereal straw).

Conclusions

The metabolism of sintofen was investigated in cereals (wheat) after foliar treatment. A residue definition for risk assessment for cereal grain is proposed as follows: sum of sintofen (free and sugar conjugates) and SC 3095 (free and sugar conjugates), expressed as sintofen. The same residue definition for risk assessment is proposed on a tentative basis for cereal straw. A residue definition for enforcement is proposed as sintofen. A validated analytical method with a LOQ of 0.01 mg/kg in wheat grain and with a LOQ of 0.05 mg/kg in wheat straw is available. Storage stability data of sintofen and metabolite SC 3095 are available for wheat grain and wheat straw.

The data on metabolism and distribution of sintofen in rotational crops indicated that the metabolism in rotational crops is similar to the pathway observed in primary crops.

Studies investigating the stability of sintofen to hydrolysis under standard conditions of pasteurisation, baking/brewing/boiling and sterilisation were not available for this review. Nevertheless, they are not necessary since residues in raw commodities were below the LOQ and the chronic exposure is below 10% of the ADI. Studies investigating the magnitude of residues in processed commodities are not required.

The available data are considered sufficient to derive tentative MRL proposals as well as risk assessment values for wheat grain and wheat straw. It is noted that MRLs were not derived to consider the potential residue uptakes in rotational crops as it is assumed that residues from rotational crops can be avoided. A mitigation measures such as ‘crop not to be rotated with a PBI shorter than 365 days’ was tentatively proposed.

Studies investigating the metabolism in livestock were conducted on lactating goats. 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.

Chronic 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 WHO cluster diet B, representing 0.1% of the ADI.

Based on these calculations, EFSA concludes that the use of sintofen results in a consumer exposure lower than the toxicological reference value. Therefore, this use is unlikely to pose a risk to consumer’s health, noting that there is still uncertainty linked to the major data gaps (residue levels of metabolite SC 1231 in cereals straw). Acute exposure calculations were not carried out because an ARfD was not deemed necessary for this active substance.

Recommendations

MRL recommendations were derived in compliance with the decision tree reported in Appendix E of the reasoned opinion (see Table 1). A tentative MRL could be derived for wheat grain (the only use
under assessment), which requires further considerations by risk managers; the following data gap was identified:

- Residue trials on F2 generation straw to confirm that no residues of metabolite SC 1231 are expected (data gap relevant for wheat grain and straw).

In addition, it was noted that significant residues may be expected in rotational crops. Based on the available data, there are indications that applying mitigation measures would allow limiting the residue uptakes to levels below the LOQ in all crops that can be grown in rotation. Therefore, the MRLs derived in this review do not take into account the potential residues from rotational crops.

When granting authorisations, Member States and risk managers are recommended to consider mitigation measures to avoid residue uptakes in rotational crops. EFSA identified a tentative option being ‘crop not to be rotated with a PBI shorter than 365 days’. However, this proposal is indicative only as it is based on the results of the confined rotational crop study. Any proposal of mitigation measures may need to be confirmed by the following data:

- Field studies investigating the magnitude of residues in rotational crops.

Table 1: Summary table

| Code number | Commodity                  | Existing EU MRL (mg/kg) | Existing CXL (mg/kg) | Outcome of the review MRL (mg/kg) | Comment |
|-------------|----------------------------|-------------------------|----------------------|----------------------------------|---------|
| 500090      | Wheat grain                | 0.01*                   | –                    | 0.01*                            | Further consideration needed<sup>(a)</sup> |
| –           | Other commodities of plant and animal origin | 0.01*                   | –                    | –                                | Further consideration needed<sup>(b)</sup> |

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

* Indicates that the MRL is set at the limit of quantification.

<sup>(a)</sup>: Tentative MRL is derived from a GAP evaluated at EU level, which is not fully supported by data but for which no risk to consumers was identified; no CXL is available (combination E–I in Appendix E).

<sup>(b)</sup>: There are no relevant authorisations or import tolerances reported at EU level; no CXL is available. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A–I in Appendix E).

References

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

EFSA (European Food Safety Authority), 2010. Conclusion on the peer review of the pesticide risk assessment of the active substance sintofen. EFSA Journal 2010;8(12):1931, 49 pp. https://doi.org/10.2903/j.efsa.2010.1931

EFSA (European Food Safety Authority), 2018a. Completeness check report on the review of the existing MRLs of sintofen prepared by EFSA in the framework of Article 12 of Regulation (EC) No 396/2005, 24 May 2018. Available online: www.efsa.europa.eu

EFSA (European Food Safety Authority), 2018b. Member States consultation report on the review of the existing MRLs of sintofen prepared by EFSA in the framework of Article 12 of Regulation (EC) No 396/2005, 17 July 2018. Available online: www.efsa.europa.eu

EURL (European Union Reference Laboratories for Pesticide Residues), 2018. Evaluation report prepared under Article 12 of Regulation (EC) No 396/2005. Analytical methods validated by the EURLs and overall capability of official laboratories to be considered for the review of the existing MRLs for sintofen, March 2018. Available online: www.efsa.europa.eu

European Commission, 1997a. Appendix A. Metabolism and distribution in plants. 7028/IV/95-rev., 22 July 1996.

European Commission, 1997b. Appendix B. General recommendations for the design, preparation and realisation of residue trials. Annex 2. Classification of (minor) crops not listed in the Appendix of Council Directive 90/642/EEC. 7029/VI/95-rev. 6, 22 July 1997.

European Commission, 1997c. Appendix C. Testing of plant protection products in rotational crops. 7524/VI/95-rev. 2, 22 July 1997.

European Commission, 1997d. Appendix E. Processing studies. 7035/VI/95-rev. 5, 22 July 1997.

European Commission, 1997e. Appendix F. Metabolism and distribution in domestic animals. 7030/VI/95-rev. 3, 22 July 1997.

European Commission, 1997f. Appendix H. Storage stability of residue samples. 7032/VI/95-rev. 5, 22 July 1997.
European Commission, 1997g. Appendix I. Calculation of maximum residue level and safety intervals. 7039/VI/95 22 July 1997. As amended by the document: classes to be used for the setting of EU pesticide maximum residue levels (MRLs). SANCO 10634/2010, finalised in the Standing Committee on the Food Chain and Animal Health at its meeting of 23–24 March 2010.

European Commission, 2000. Residue analytical methods. For pre-registration data requirement for Annex II (part A, section 4) and Annex III (part A, section 5 of Directive 91/414. SANCO/3029/99-rev. 4.

European Commission, 2010a. Classes to be used for the setting of EU pesticide Maximum Residue Levels (MRLs). SANCO 10634/2010-rev. 0, Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting of 23–24 March 2010.

European Commission, 2010b. Residue analytical methods. For post-registration control. SANCO/825/00-rev. 8.1, 16 November 2010.

European Commission, 2013. Guidance document on the procedures for submission and assessment of confirmatory information following approval of an active substance in accordance with Regulation (EC) No 1107/2009. SANCO 5634/2009-rev. 6.1.

European Commission, 2014. Review report for the active substance sintofen. Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 11/03/2011 in view of the inclusion of sintofen in Annex I of Council Directive 91/414/EEC. SANCO/10232/2011-rev 1, 10 October 2014.

European Commission, 2017. Appendix D. Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs. 7525/VI/95-rev.10.3, June 2017

FAO (Food and Agriculture Organization of the United Nations), 2009. Submission and evaluation of pesticide residues data for the estimation of Maximum Residue Levels in food and feed. Pesticide Residues. 2nd Ed. FAO Plant Production and Protection Paper 197, 264 pp.

France, 2007. Draft assessment report on the active substance sintofen prepared by the rapporteur Member State France in the framework of Council Directive 91/414/EEC, March 2007.

France, 2010a. Additional report to the draft assessment report on the active substance sintofen prepared by the rapporteur Member State France in the framework of Commission Regulation (EC) No 33/2008, January 2010. Available online: www.efsa.europa.eu

France, 2010b. Final addendum to the additional report on the active substance sintofen prepared by the rapporteur Member State France in the framework of Commission Regulation (EC) No 33/2008, compiled by EFSA, September 2010. Available online: www.efsa.europa.eu

France, 2018. Evaluation report prepared under Article 12.1 of Regulation (EC) No 396/2005. Review of the existing MRLs for sintofen, February 2018. Available online: www.efsa.europa.eu

OECD (Organisation for Economic Co-operation and Development), 2011. OECD MRL calculator: spreadsheet for single data set and spreadsheet for multiple data set, 2 March 2011. In: Pesticide Publications/Publications on Pesticide Residues. Available online: http://www.oecd.org

OECD (Organisation for Economic Co-operation and Development), 2013. Guidance document on residues in livestock. In: Series on Pesticides No 73. ENV/JM/MONO(2013)8, 04 September 2013.

**Abbreviations**

- **a.s.** active substance
- **ADI** acceptable daily intake
- **AR** applied radioactivity
- **ARfD** acute reference dose
- **BBCH** growth stages of mono- and dicotyledonous plants
- **BVL** Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, Germany
- **bw** body weight
- **CF** conversion factor for enforcement residue definition to risk assessment residue definition
- **CXL** codex maximum residue limit
- **DAR** draft assessment report
- **DAT** days after treatment
- **DB** dietary burden
- **DM** dry matter
- **DT90** period required for 90% dissipation (define method of estimation)
- **eq** residue expressed as a.s. equivalent
- **EURLs** European Union Reference Laboratories for Pesticide Residues (former CRLs)
- **FAO** Food and Agriculture Organization of the United Nations
- **GAP** Good Agricultural Practice
- **HR** highest residue
- **IEDI** international estimated daily intake
- **ILV** independent laboratory validation

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| Acronym | Abbreviation | Definition |
|---------|--------------|------------|
| 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 |
| NEU     | northern European Union |
| OECD    | Organisation for Economic Co-operation and Development |
| PBI     | plant-back interval |
| PEC     | predicted environmental concentration |
| PF      | processing factor |
| PHI     | preharvest interval |
| PRIMo   | (EFSA) Pesticide Residues Intake Model |
| PROFile | (EFSA) Pesticide Residues Overview File |
| RA      | risk assessment |
| RD      | residue definition |
| RMS     | rapporteur Member State |
| SANCO   | Directorate-General for Health and Consumers |
| SC      | suspension concentrate |
| SEU     | southern European Union |
| SMILES  | simplified molecular-input line-entry system |
| SL      | soluble concentrate |
| STMR    | supervised trials median residue |
| TRR     | total radioactive residue |
| WHO     | World Health Organization |
## Appendix A – Summary of authorised uses considered for the review of MRLs

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

| Crop and/or situation | MS or country | F G or I(a) | Pests or Group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days)(d) | Remarks |
|-----------------------|---------------|-------------|-----------------------------------|-------------|-------------|--------------------------------|---------------|---------|
| Wheat                 | CZ, DE, FR, HU, SK | F           | Wheat hybridising agent           | SL 100 g/L | Foliar treatment – spraying | 30–33 1 | – – 1,500 n.a. | For hybrid seeds production only; 1 application every 2 years. On average 50% of the field is treated. Regulatory restriction: wheat treated with sintofen (i.e. F1 grains and straws) shall not enter the food or feed chain. (European Commission, 2014) |

**GAP:** Good Agricultural Practice; **BBCH:** growth stages of mono- and dicotyledonous plants; **PHI:** preharvest interval; **NEU:** northern European Union; **SEU:** southern European Union; **a.s.:** active substance; **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 preharvest interval.
## A.2. Authorised uses in southern outdoor EU

| Crop and/or situation | MS or country | F | G or I(a) | Pests or Group of pests controlled | Preparation | Application | Application rate per treatment | PHI (days)(d) | Remarks |
|-----------------------|---------------|---|-----------|-----------------------------------|-------------|-------------|--------------------------------|--------------|---------|
| Wheat FR F            |               |   |           | Wheat hybridising agent           | SL          | Foliar treatment – spraying       | 30–33           | 1       | 1500    | n.a. For hybrid seeds production only; 1 application every 2 years. On average 50% of the field is treated. Regulatory restriction: wheat treated with sintofen (i.e. F₁ grains and straws) shall not enter the food or feed chain. (European Commission, 2014) |

GAP: Good Agricultural Practice; BBCH: growth stages of mono- and dicotyledonous plants; PHI: pre-harvest interval; NEU: northern European Union; SEU: southern European Union; a.s.: active substance; 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 preharvest interval.
# Appendix B – List of end points

## B.1. Residues in plants

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

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

| Primary crops (available studies) | Crop groups | Crop(s) | Application(s) | Sampling (DAT)(a) |
|----------------------------------|-------------|---------|----------------|-------------------|
| Cereals/grass crops              | Wheat       | Foliar at BBCH 33, 3,000 g a.s./ha | 14              |
|                                  |             | Foliar at BBCH 31, 1,500 g a.s./ha | 100             |
|                                  |             | Foliar at BBCH 32–37, ca 1,200–1,400 g a.s./ha | 42, 93 |

First studies: sintofen labelled on the chlorophenyl ring (France, 2010b)
Third study: sintofen labelled on the chlorophenyl and cinnoline(phenyl) rings (France, 2018)

(a): sampling on F₁ generation grain and straw is deemed acceptable to depict the metabolism pathway of sintofen on F₂ generation

| Rotational crops (available studies) | Crop groups | Crop(s) | Application(s) | PBI (DAT) |
|-------------------------------------|-------------|---------|----------------|-----------|
| Leafy vegetables                    | Lettuce     | Bare soil, 1.15 mg a.s./kg soil | 30, 104, 368 |
| Root crops                          | Radish      | Bare soil, 1.15 mg a.s./kg soil | 30, 90, 368 |
| Cereal (small grain)                | Wheat       | Bare soil, 1.15 mg a.s./kg soil | 30, 90, 368 |

Sintofen labelled on the chlorophenyl ring and cinnoline(phenyl) rings; concentration reflects accumulation PEC plateau (France, 2018)

| Processed commodities (hydrolysis study) | Conditions                        | Investigated? |
|------------------------------------------|-----------------------------------|---------------|
|                                        | Pasteurisation (20 min, 90°C, pH 4) | No            |
|                                        | Baking, brewing and boiling (60 min, 100°C, pH 5) | No            |
|                                        | Sterilisation (20 min, 120°C, pH 6) | No            |

No studies available and not required.
Can a general residue definition be proposed for primary crops? | No (only for cereals)
---|---
Rotational crop and primary crop metabolism similar? | Yes
Residue pattern in processed commodities similar to residue pattern in raw commodities? | Not applicable
Plant residue definition for monitoring (RD-Mo) | sintofen [restricted to cereals]
Plant residue definition for risk assessment (RD-RA) | sum of sintofen (free and sugar conjugates) and SC 3095 (free and sugar conjugates), expressed as sintofen [restricted to cereal grain; tentative for cereals straw]
Conversion factor (monitoring to risk assessment) | See Appendix B.1.2.1
Methods of analysis for monitoring of residues (analytical technique, crop groups, LOQs) | LC–MS/MS (EFSA, 2010):
- LOQ: 0.01 mg/kg (dry commodities; wheat grain)
- LOQ: 0.05 mg/kg (wheat straw) LC–MS/MS (EURL, 2018):
- Method EN 15662:2008 validated in high water and high acid and dry content commodities
- Method BVL L 13.04-5:2013-08 (QuOil method) validated in high oil content commodities
- LOQ: 0.01 mg/kg (for the four main plant matrices)

a.s.: active substance; DAT: days after treatment; BBCH: growth stages of mono- and dicotyledonous plants; PBI: plant-back interval; PEC: predicted environmental concentration; LC–MS/MS: liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

B.1.1.2. Stability of residues in plants

| Plant products (available studies) | Category | Commodity | T (°C) | Stability (Months) |
|---|---|---|---|---|
| Dry/starch | Wheat grain | –20 | 18 |
| Specific matrices | Wheat straw | –20 | 18 |

Source: EFSA (2010)
Stability demonstrated for sintofen and metabolite SC 3095 separately.
## B.1.2. Magnitude of residues in plants

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

| Crop       | Region/ indoor\(^{(a)}\) | Residue levels observed in the supervised residue trials relevant to the supported GAPs (mg/kg)                                                                 | Recommendations/comments (OECD calculations)                                                                 | MRL proposals (mg/kg) | HR\(_{Mo}\) (mg/kg)\(^{(b)}\) | STMR\(_{Mo}\) (mg/kg)\(^{(c)}\) | CF\(^{(d)}\) |
|------------|--------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------|--------------------------|--------------------------|--------|
| Wheat      | NEU                      | **Mo:** 3 × < 0.01 **RA:** 3 × < 0.02                                                                                                                                                     | Trials compliant with GAP (France, 2010b); EFSA, 2010. Data on F\(_2\) grains                                                                 | 0.01*\(^{(e)}\) (tentative) | < 0.01                   | < 0.01                   | 1       |
|            | SEU                      | –                                                                                                                                                                                            | A no-residue situation is expected for F\(_2\) grains. Residues are below the LOQ in all available NEU trials thus NEU data are considered sufficient and no SEU trials are required | 0.01*\(^{(e)}\) (tentative) | < 0.01                   | < 0.01                   | 1       |
| Wheat      | NEU                      | **Mo:** 3 × < 0.05 **RA:** 3 × < 0.1                                                                                                                                                       | Trials compliant with GAP (France, 2010b); EFSA, 2010. Data on F\(_2\) wheat straw                                                                 | 0.05*\(^{(f)}\) (tentative) | < 0.05                   | < 0.05                   | 1       |
|            | SEU                      | –                                                                                                                                                                                            | A no-residue situation is expected for F\(_2\) straw. Residues are below the LOQ in all available NEU trials thus NEU data are considered sufficient and no SEU trials are required | 0.05*\(^{(f)}\) (tentative) | < 0.05                   | < 0.05                   | 1       |

GAP: Good Agricultural Practice; OECD: Organisation for Economic Co-operation and Development; MRL: maximum residue level.

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

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

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

*\(^{(d)}\): Conversion factor for risk assessment; median of the individual conversion factors at the supported PHI for each residues trial.

*\(^{(e)}\): MRL is tentative because information on the residue levels of SC 1231 in F\(_2\) generation is needed.

*\(^{(f)}\): Tentative MRLs are derived for feed items in view of the future need to set MRLs on these commodities.
B.1.2.2. Residues in succeeding crops

| Study Type                          | Description                                                                 | Results                                                                                                                                                                                                 |
|-------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Confinement rotational crop study   | Quantitative aspect                                                        | Up to 90/104 DAT, there were significant levels of sintofen in radish foliage and of metabolite SC 3095 (free and conjugated) in wheat hay, wheat straw and wheat grain. At 368 DAT, the only significant residues were of metabolite SC 3095 in wheat straw (0.024–0.022 mg eq/kg) |
| Field rotational crop study         | Not available. A cold rotational field study would allow a better picture of the magnitude of residues in rotational crops |                                                                                                                                                                                                       |

DAT: days after treatment.

B.1.2.3. Processing factors

Not available and not required.

B.2. Residues in livestock

### Relevant groups

| Relevant groups | Dietary burden expressed in mg/kg bw per day | mg/kg DM | Most critical diet(a) | Most critical commodity(a) | Trigger exceeded (Y/N) |
|----------------|----------------------------------------------|---------|-----------------------|---------------------------|------------------------|
| Cattle (all diets) | 0.0008 Max. 0.0008 Med. 0.02 Max. 0.02 | Cattle (dairy) | Wheat, straw | No |
| Cattle (dairy only) | 0.0008 Max. 0.0008 Med. 0.02 Max. 0.02 | Cattle (dairy) | Wheat, straw | No |
| Sheep (all diets) | 0.0014 Max. 0.0014 Med. 0.03 Max. 0.03 | Sheep (lamb) | Wheat, straw | No |
| Sheep (ewe only) | 0.0011 Max. 0.0011 Med. 0.03 Max. 0.03 | Sheep (ram/ewe) | Wheat, straw | No |
| Swine (all diets) | 0.0003 Max. 0.0003 Med. 0.01 Max. 0.01 | Swine (finishing) | Wheat, milled by-products | No |
| Poultry (all diets) | 0.0011 Max. 0.0011 Med. 0.02 Max. 0.02 | Poultry (layer) | Wheat, straw | No |
| Poultry (layer only) | 0.0011 Max. 0.0011 Med. 0.02 Max. 0.02 | Poultry (layer) | Wheat, straw | No |

bw: body weight; DM: dry matter.
(a): Calculated for the maximum dietary burden.

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 per day) | Duration (days) | N rate/comment |
|-------------------------------|--------|--------------------------|-----------------|----------------|
| Lactating goat               | 0.01   | 7                        | 7N (compared to sheep all diets) |
|                               | 1.23   | 7                        | to sheep 878N (compared all diets) |

Source: France, 2010b
### B.2.1.2. Stability of residues in livestock

| Animal products (available studies) | Animal | Commodity | T (°C) | Stability (Months/years) |
|-------------------------------------|--------|-----------|--------|-------------------------|
|                                     |        |           |        |                         |
|                                     |        |           |        | No studies 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

MRLs are not necessary as all dietary burdens were found to be below the trigger value assuming that mitigation measures to avoid residue uptakes in rotational crops would be sufficient and implemented.

### B.3. Consumer risk assessment

| ADI | 0.091 mg/kg bw per day (EFSA, 2010) |
|-----|-----------------------------------|
| Highest IEDI, according to EFSA PRIMO | 0.1% ADI (WHO, cluster diet B) |
| Assumptions made for the calculations | The calculation was based on the median residue levels in wheat and assuming that mitigation measures to avoid residues in rotational crops would be sufficient and implemented. The contributions of commodities where no GAP was reported in the framework of this review were not included |

**ADI**: acceptable daily intake; **bw**: body weight; **IEDI**: international estimated daily intake; **PRIMO**: (EFSA) Pesticide Residues Intake Model; **WHO**: World Health Organization; **GAP**: Good Agricultural Practice.

### B.4. Proposed MRLs

| Code number | Commodity | Existing EU MRL (mg/kg) | Existing CXL (mg/kg) | Outcome of the review | Comment |
|-------------|-----------|-------------------------|----------------------|-----------------------|---------|
| 500090      | Wheat grain | 0.01*                   | –                    | 0.01*                 | Further consideration needed(a) |
| –           | Other commodities of plant and animal origin | 0.01* | – | – | Further consideration needed(b) |

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

* indicates that the MRL is set at the limit of quantification.

(a): Tentative MRL is derived from a GAP evaluated at EU level, which is not fully supported by data but for which no risk to consumers was identified; no CXL is available (combination E–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(EU1)**

#### Sintofen

| Toxicological end points | Code no. | Proposed LOQ | ADI (mg/kg bw) | ARfD (mg/kg bw) | Source of ADI | Source of ARfD | Year of evaluation |
|--------------------------|---------|--------------|----------------|----------------|---------------|---------------|-------------------|
|                          |         |              | 0.091          | n.n.           | EFSA         | EFSA         | 2010              |

#### Chronic risk assessment – refined calculations

| Commodity/group of commodities | TMDI (range) in % of ADI | Highest contributor to MS diet (in % of ADI) | 2nd contributor to MS diet (in % of ADI) | 3rd contributor to MS diet (in % of ADI) | pTMRLs at LOQ (in % of ADI) |
|-------------------------------|--------------------------|-----------------------------------------------|------------------------------------------|------------------------------------------|----------------------------|
| Wheat | 0.1 | WHO Cluster diet B | 0.1 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.1 | IT kids/toddler | 0.1 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.1 | WHO cluster diet D | 0.1 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.1 | DK child | 0.1 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.1 | NL child | 0.1 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | ES child | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | IT adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | DE child | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | WHO cluster diet E | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | PT General population | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | UK Toddler | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | WHO Cluster diet F | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | FR all population | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | SE regional population 90th percentile | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | WHO regional European diet | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | FR toddler | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | UK Infant | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | ES adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | E adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | NL general | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | UK vegetarian | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | DK adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | UK Adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | LT adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | FI. adult | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | FR plant | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | FRUIT (FRESH OR FROZEN) |
|      | 0.0 | PL: general population | 0.0 | Wheat | FRUIT (FRESH OR FROZEN) | 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 sintofen is unlikely to present a public health concern.
Acute risk assessment/children – refined calculations

Acute risk assessment is not necessary.

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.

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

No of critical MRLs (IESTI 1): ---

No of critical MRLs (IESTI 2): ---

| Commodity | ARfD/ADI | pTMRL/Threshold MRL (mg/kg) |
|-----------|----------|-----------------------------|
| Processed commodities | --- | --- |
| Unprocessed commodities | --- | --- |

Conclusion:

As no ARfD was considered necessary, it is concluded that the short-term intake of sintofen residues is unlikely to present a public health concern.

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

**pTMRL: provisional temporary MRL for processed commodity.

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

Acute risk assessment/adults/general population – refined calculations
Appendix D – Input values for the exposure calculations

### D.1. Livestock dietary burden calculations

| Feed commodity           | Median dietary burden | Maximum dietary burden |
|--------------------------|-----------------------|------------------------|
|                          | Input value (mg/kg)   | Comment                | Input value (mg/kg) | Comment          |
| **Risk assessment residue definition** – sum of sintofen (free and sugar conjugates) and SC3095 (free and sugar conjugates), expressed as sintofen |                       |                        |                    |
| Wheat, grain             | 0.01*                 | STMR                   | 0.01*               | STMR             |
| Wheat, distiller’s grain (dry) | 0.01*                 | STMR (default PF not applied) | 0.01*               | STMR (default PF not applied) |
| Wheat gluten, meal       | 0.01*                 | STMR (default PF not applied) | 0.01*               | STMR (default PF not applied) |
| Wheat, milled by-pdts    | 0.01*                 | STMR (default PF not applied) | 0.01*               | STMR (default PF not applied) |
| Wheat, straw             | 0.05*                 | STMR                   | 0.05*               | HR               |

STMR: supervised trials median residue; HR: highest residue; PF: processing factor.
*: Indicates that the input value is proposed at the limit of quantification.

### D.2. Consumer risk assessment

| Commodity     | Chronic risk assessment |
|---------------|-------------------------|
|               | Input value (mg/kg)     | Comment               |
| **Risk assessment residue definition** – sum of sintofen (free and sugar conjugates) and SC3095 (free and sugar conjugates), expressed as sintofen |                       |                        |
| Wheat, grain  | 0.01*                   | STMR (tentative)      |

STMR: supervised trials median residue.
*: 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 derived in Section 3?
      - Yes
        - MRL fully supported by data?
          - Yes
            - MRL is recommended.
          - No
            - Not considered for the RA.
        - No
          - Tentative median/highest values are included in the RA.
          - Risk identified?
            - Yes
              - Fall-back MRL available?
                - Yes
                  - MRL is recommended.
                - No
                  - Not considered for the RA.
            - No
              - MRL is recommended.

- No
  - Specific LOQ or default MRL?
    - Yes
      - Specific LOQ or default MRL?
        - Yes
          - Specific LOQ or default MRL?
            - Yes
              - MRL is recommended.
            - No
              - MRL is recommended.
        - No
          - MRL is recommended.
    - No
      - MRL is recommended.

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

- Not considered for the RA.
- Current EU MRL is included in the RA.
  - Risk identified?
    - Yes
      - Fall-back MRL available?
        - Yes
          - MRL is recommended.
        - No
          - MRL is recommended.
    - No
      - MRL is recommended.
  - No
    - MRL is recommended.

- Tentative median/highest values are included in the RA.
  - Risk identified?
    - Yes
      - Fall-back MRL available?
        - Yes
          - MRL is recommended.
        - No
          - MRL is recommended.
    - No
      - MRL is recommended.

- Median/highest values are included in the RA.
  - Fall-back MRL available?
    - Yes
      - MRL is recommended.
    - No
      - MRL is recommended.

Recommendations resulting from EU authorisations and import tolerances

- Specific LOQ or default MRL?
  - Yes
    - Specific LOQ or default MRL?
      - Yes
        - Specific LOQ or default MRL?
          - Yes
            - MRL is recommended.
          - No
            - MRL is recommended.
      - No
        - MRL is recommended.
  - No
    - MRL is recommended.

- MRL derived in Section 3?
  - Yes
    - MRL fully supported by data?
      - Yes
        - MRL is recommended.
      - No
        - MRL is recommended.
  - No
    - MRL is recommended.

- Fall-back MRL available?
  - Yes
    - MRL is recommended.
  - No
    - MRL is recommended.

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

- CXL available?
  - Yes: RD comparable?
    - Yes: CXL higher?
      - Yes: CXL is included in the RA?
        - Yes: Codex median/highest residues included in the RA?
    - No: Input values for the RA remain unchanged.
  - No: Input values for the RA remain unchanged.

Consumer risk assessment with consideration of the existing CXL

- RD comparable?
  - Yes: CXL higher?
    - Yes: CXL is included in the RA?
      - Yes: Codex median/highest residues included in the RA?
    - No: Input values for the RA remain unchanged.
  - No: Risk identified?
    - Yes: Risk identified?
    - No: Input values for the RA remain unchanged.

Recommendations with consideration of the existing CXL

1. Maintain EU recommendation indicating that no CXL is available.
2. Maintain EU recommendation indicating CXL is not compatible.
3. Maintain EU recommendation indicating that CXL is covered.
4. Maintain EU recommendation; higher CXL is not safe for consumer.
5. Maintain current EU recommendation; higher CXL is not safe for consumer.
6. Maintain EU recommendation; higher CXL is covered as well.

Result EU assessment

- Yes: Comparison of the EU recommendation with the existing CXL
- No: Consumer risk assessment with consideration of the existing CXL
### Appendix F – Used compound codes

| Code/trivial name(a) | IUPAC name/SMILES notation/InChiKey(b) | Structural formula(c) |
|----------------------|---------------------------------------|-----------------------|
| Sintofen (SC 2053)   | 1-(4-chlorophenyl)-1,4-dihydro-5-(2-methoxyethoxy)-4-oxocinnoline-3-carboxylic acid<br>\( \text{O=C(O)C1=NN(c2ccc(Cl)cc2)c2cccc(OCCOC)c2C1=O} \)<br>QLMN{\text{CUHSDAGQGT}}-{\text{UHFFFAOYS}}-N | ![Structural formula](image) |
| Desmethyl sintofen (SC 3095) | 1-(4-chlorophenyl)-5-(2-hydroxyethoxy)-4-oxo-1,4-dihydrocinnoline-3-carboxylic acid<br>\( \text{O=C(O)C1=NN(c2ccc(Cl)cc2)c2cccc(OCCO)c2C1=O} \)<br>{\text{YBJKMXUES}}RQBN-{\text{UHFFFAOYS}}-N | ![Structural formula](image) |
| SC 1231              | 1-(4-chlorophenyl)-5-hydroxy-4-oxo-1,4-dihydrocinnoline-3-carboxylic acid<br>\( \text{O=C(O)C1=NN(c2ccc(Cl)cc2)c2cccc(O)c2C1=O} \)<br>{\text{YHEMLIOLXQLDLV}}-{\text{UHFFFAOYS}}-N | ![Structural formula](image) |

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

(a): The metabolite name in bold is the name used in the conclusion.
(b): ACD/Name 2015 ACD/Labs 2015 Release (File version N20E41, Build 75170, 19 December 2014).
(c): ACD/ChemSketch 2015 ACD/Labs 2015 Release (File version C10H41, Build 75059, 17 December 2014).