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Targeted review of maximum residue levels (MRLs) for azocyclotin and cyhexatin

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Abstract

In accordance with Article 43 of Regulation (EC) 396/2005, EFSA received a request from the European Commission to review the existing maximum residue levels (MRLs) for the non-approved active substances azocyclotin and cyhexatin in view of the possible lowering of these MRLs. EFSA investigated the origin of the current EU MRLs. For existing EU MRLs that reflect previously authorised uses in the EU, or that are based on obsolete Codex Maximum Residue Limits, or import tolerances that are not required any longer, EFSA proposed the lowering to the limit of quantification. EFSA performed an indicative chronic and acute dietary risk assessment for the revised list of MRLs to allow risk managers to take the appropriate decisions. For some commodities under assessment, further risk management discussions are required to decide which of the risk management options proposed by EFSA should be implemented in the EU MRL legislation.

Keywords: consumer risk assessment, toxicological evaluation, residue definitions, MRL setting, azocyclotin, cyhexatin, non-approved active substance

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Summary

The European Commission submitted a request to EFSA for a targeted review of maximum residue limits (MRLs) for 10 active substances no longer approved in the EU, but for which MRLs greater than the limit of quantification (LOQ) are still in place and for which Member States have identified potential consumer health risks. Separate reasoned opinions should be provided in accordance with Article 43 of Regulation (EC) 396/2005, for each of the substances included in this mandate, two of them being azocyclotin and cyhexatin.

In accordance with the terms of reference, EFSA investigated the origin of the current EU MRLs for azocyclotin and cyhexatin, and whether they are sufficiently substantiated. An EU MRL is considered substantiated if it is sufficiently supported by data and established for uses still authorised or based on Codex Maximum Residue Limit (CXL) or import tolerance that are still in place and relevant. Accordingly, MRLs that were derived for previously authorised EU uses are obsolete and should be lowered to the LOQ. For those commodities for which the existing EU MRLs are based on a CXL, EFSA investigated whether the CXLs are still in place and whether they are sufficiently supported by data. Obsolete or insufficiently supported Codex MRLs are also candidates for being lowered to the LOQ. To identify possible import tolerances, EFSA consulted Member States on Good Agricultural Practices authorised in third countries that were evaluated at national level which might justify maintaining certain MRLs as import tolerances. Following this Member State consultation, EFSA concluded that none of the existing EU MRLs for azocyclotin and cyhexatin has been established as an import tolerance. EFSA also screened the quality of the toxicological reference values (TRVs) derived at EU level and by the Joint Meeting on Pesticide residues (JMPR). As EFSA identified critical issues related to the available toxicological database, EFSA organised an expert consultation (Pesticides Peer Review Teleconference 92) to discuss the toxicological profile and the TRVs for azocyclotin and cyhexatin.

EFSA prepared a draft reasoned opinion that was shared with Member States and the European Reference Laboratories (EURLs) for consultation via a written procedure. Comments received were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

The metabolism of azocyclotin and cyhexatin in plants and animals was previously investigated in the framework of the EU evaluation (Italy, 2008a,b) as well as by JMPR (FAO, 2005a,b). According to the results of the metabolism studies assessed, the residue definition for enforcement and risk assessment, both for plant and animal products, is the sum of azocyclotin and cyhexatin, expressed as cyhexatin.

Analytical methods are available for the enforcement of the proposed residue definition in high water and high acid content matrices with an LOQ of 0.01 mg/kg, in orange dry pulp with an LOQ of 0.02 mg/kg, in apple dry pomace with an LOQ of 0.05 mg/kg and in high oil content matrices with an LOQ of 0.1 mg/kg. Azocyclotin and cyhexatin residues can be enforced in food of animal origin with an LOQ of 0.1 mg/kg in muscle and liver. No method is available for the enforcement of residues in kidney, fat, milk and eggs. According to the EURLs, a QuEChERS multi-residue analytical method with an LOQ of 0.01 mg/kg for the routine analysis of azocyclotin and cyhexatin residues in high water, high acid and dry commodities. Based on the experience gained with these matrices, a default LOQ of 0.01 mg/kg in all commodities of animal origin except fat and a default LOQ of 0.02 mg/kg in fat and in high oil content matrices is also deemed achievable to monitor azocyclotin and cyhexatin residues.

The origin of all current MRLs set for azocyclotin and cyhexatin was investigated, and further risk management discussions are required to decide whether the existing EU MRL for apples and wine grapes should be maintained or lowered to the LOQ.

A screening of the quality of the group TRVs proposed by the RMS and of those established by the JMPR was performed, and the set of toxicological studies used to derive these TRVs was assessed according to the current standards. As critical issues were identified, a Member States experts' consultation took place. The experts concluded that the TRVs proposed by the RMS and derived by JMPR cannot be confirmed for azocyclotin and cyhexatin since the genotoxicity potential of either active substance was considered inconclusive, the data available were of insufficient reliability compared to current standards, and uncertainty factors could not be established. Accordingly, the acceptable daily intake (ADI) and acute reference dose (ARfD) used for the setting of MRLs do not comply with the current scientific standards. Therefore, EFSA recommends withdrawing these TRVs. The following data would be required to finalise the toxicological assessment which is a pre-requisite to derive robust TRVs:

- additional studies to conclude on the genotoxic potential of azocyclotin and cyhexatin;
- assessment of the validity of analytical methods used in feed, body fluids and tissues, air and any additional matrices used in support of the toxicological studies;
- literature search;
- additional toxicological data to perform an ED assessment;
- comparative *in vitro* metabolism study on animal species used in pivotal studies and on human material;
- full re-evaluation of the toxicological data package and reporting relevant details on the studies and the results in accordance with the current guidelines.

Chronic and acute exposure calculations were performed using revision 3.1 of PRIMo, considering commodities for which the existing EU MRLs were found to be sufficiently substantiated, while all CXLs/MRLs that could be no longer substantiated (upon risk managers' decision) were proposed to be lowered to the appropriate LOQ, as well as all other commodities for which no GAP was reported under this review. Comparing to the EU TRVs, no exceedances were observed, and the highest chronic exposure represented 51% of the ADI (NL toddler). The highest acute exposure amounted to 86% of the ARfD (apples). Nevertheless, EFSA emphasises that as the toxicological assessment revealed deficiencies regarding the toxicological studies available for azocyclotin and cyhexatin and considering that EU TRVs do not meet the current scientific standards, the indicative risk assessment cannot be finalised and results presented under the current review are indicative only.

Due to the deficiencies identified regarding the toxicological studies available for azocyclotin and cyhexatin, none of the existing EU MRLs listed in the summary table below are recommended for inclusion in Annex II to the Regulation. If a decision on the withdrawing of TRVs is taken, EFSA recommends that risk managers discuss whether all MRLs currently implemented in EU Regulation should be lowered to the respective LOQs.

Summary table:

Code[(a)]	Commodity	Existing MRL[(b)] (mg/kg)	Outcome of the review	
			MRL proposal (mg/kg)	Comment
Residue definition for enforcement (plants and animal products): Sum of azocyclotin and cyhexatin, expressed as cyhexatin				
0110020	Oranges	0.2	0.2 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards).
0130010	Apples	0.2	0.2 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as: – the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards) – this MRL was initially based on a CXL derived from European uses that are no longer authorised.

Code[(a)]	Commodity	Existing MRL[(b)] (mg/kg)	Outcome of the review	
			MRL proposal (mg/kg)	Comment
0151020	Wine grapes	0.3	0.3 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as: – the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards) – this MRL was initially based on a CXL derived from European uses that are no longer authorised.

MRL: maximum residue limit; CXL: Codex residue limit; LOQ: limit of quantification; TRV: toxicological reference value; GAP: good agricultural practice.
(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
(b): MRL currently set under Regulation (EU) No 899/2012.

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Background

In March 2021, a Member State submitted to the European Commission the results of a screening performed on all maximum residue levels (MRLs) of active substances used in plant protection products that are not approved in the EU. The list contained 904 substances; for 297 of them, at least one MRL was set at a level above the limit of quantification (LOQ).

For 219 of these substances, the MRLs are not related to the uses of the substances in plant protection products (e.g. MRLs reflect the use of biocides or veterinary medical product, or MRLs are set to account for their occurrence in certain food due to environmental persistence, or their natural occurrence). For the other 78 substances, the MRLs were established either based on formerly approved uses in the EU, on import tolerance requests, or on Codex maximum residue limits (CXLs).

Some of these substances were never approved in the EU, or their approval was withdrawn before 2008, and therefore they did not fall within the scope of the systematic review of all existing MRLs under Article 12 of Regulation (EC) No 396/2005[1].

A second Member State conducted additional analysis, identifying potential consumer risk for some of the MRLs set for these active substances.

Based on these analyses, the European Commission conducted a prioritisation exercise to identify substances for which existing MRLs should be reviewed with high priority. The prioritisation was also discussed and agreed with Member States during several meetings of the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), section Phytopharmaceuticals – Pesticides residues (September 2021,[2] November 2021,[3] and February 2022[4]). The SCoPAFF agreed that ten active substances, for which potential consumer risks were identified, should be assessed by EFSA as a priority. Two of the substances identified for being assessed with high priority are azocyclotin and cyhexatin.

The European Commission proposed to mandate EFSA to provide a targeted review of MRLs for the substances concerned without delay. Due to the urgency of the subject, EFSA was invited to consider, if appropriate, delivering a separate reasoned opinion for each of the substances included in this mandate, as to be able to start providing outcomes to the Commission as soon as possible and successively. In this reasoned opinion, EFSA covered the targeted review of the MRLs for azocyclotin and cyhexatin.

Terms of Reference (as provided by the requestor)

EFSA was requested by the European Commission, according to Article 43 of Regulation (EC) No 396/2005, to prepare a reasoned opinion on azocyclotin and cyhexatin. In particular, the following tasks should be performed:

1) to investigate the origin of the current EU MRLs (e.g. MRL based on formerly approved uses in the EU, on import tolerance requests, or on CXLs). This analysis should allow to verify if the CXLs/import tolerances are still justified[5] and to identify MRLs that do not correspond to import tolerances or currently established CXLs (non-verified CXL/import tolerances);
2) to consult Member States on information about Good Agricultural Practices authorised in third countries and already evaluated at MS level, which might support maintaining the existing import tolerances or setting of new (lowered) import tolerances, if this is necessary in view of consumer protection;
3) to identify fall-back MRLs for MRLs that do not correspond to a verified CXLs/import tolerance; these fall-back MRLs could be either a lower import tolerance or a lower CXL established more recently. If no fall-back MRL can be identified, the MRL should be considered for lowering to the appropriate LOQ;

[1] Regulation (EC) No 396/2005 of the Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.03.2005, p. 1–16.
[2] Standing Committee on Plants, Animals, Food and Feed Section Phytopharmaceuticals – Pesticide Residues 23–24 September 2021 (https://food.ec.europa.eu/system/files/2021-10/sc_phyto_20210923_ppr_sum.pdf).
[3] Standing Committee on Plants, Animals, Food and Feed Section Phytopharmaceuticals – Pesticide Residues 22–23 November 2021 (https://food.ec.europa.eu/system/files/2021-12/sc_phyto_20211122_ppr_sum_0.pdf).
[4] Standing Committee on Plants, Animals, Food and Feed Section Phytopharmaceuticals – Pesticide Residues 22–23 February 2022 (https://food.ec.europa.eu/system/files/2022-08/sc_phyto_20220222_ppr_sum.pdf).
[5] A CXL is considered justified if it is still in place (i.e. if it has not been withdrawn). An import tolerance is to be considered justified if the GAP in the country of origin is still authorised and the MRL in the country of origin is established at a level corresponding to the EU MRL (taking into account the potential difference in the RDs).

4) to consult the EU Reference Laboratories (EURLs) on the LOQs achievable during routine analyses for all commodities;
5) to perform an indicative screening of the chronic and acute consumer exposure related to the existing EU MRLs reflecting the verified CXLs/import tolerances, fall-back MRLs and/or proposed revised LOQ MRLs, using the newest version of the Pesticide Residues Intake Model (PRIMo) based on the available residue definitions for risk assessment and, if not available, residue definitions for enforcement derived at EU level or by JMPR. The following scenarios should be calculated:
    a) Scenario 1:
        i) Values at the appropriate LOQ: all MRLs that are based on former EU uses and all CXLs that were revoked by the Codex Committee on Pesticide Residues (CCPR) should be lowered to the appropriate LOQ;
        ii) Non-LOQ values to be considered: CXLs that were previously taken over in EU legislation, CXLs that were covered by still existing (higher) EU MRLs to be considered at the value of the CXL, MRLs based on existing import tolerances;
    b) Scenario 2:
        i) Like scenario 1, but lowering all CXLs that were evaluated by EFSA before and including 2009[6] and all import tolerances established before and including 2007,[7] respectively, to the appropriate LOQ.
6) to derive the input values for commodities of animal origin for the consumer exposure calculation from the relevant assessment where the MRLs for animal products were derived. However, if the respective risk assessment values (HR/STMR) cannot be retrieved from the available sources, the exposure shall be calculated with the existing MRL. If the existing MRL is no longer justified and no fall-back MRL can be retrieved, the existing MRL should be considered for being lowered to the LOQ; in this case the risk assessment screening should be performed with the LOQ;
7) to examine the available information in order to screen the quality of the toxicological reference values (TRVs) set at EU level and of those established by JMPR. This screening should also consider the completeness of the set of toxicological studies used to derive the TRVs, as to assess if it would be acceptable according to the current standards. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties;
8) to examine the available information in order to screen the quality of the residue definitions for risk assessment set at EU level and of those established by JMPR. In case deficiencies are identified, these should be highlighted along with the resulting uncertainties;
9) to compare the indicative chronic and acute dietary exposure to the toxicological reference values derived at EU level or, if not available, to the toxicological reference values derived by JMPR;
10) to report information on the classification of the substance under the CLP Regulation[8] and whether the active substance meets the criteria for endocrine disruptors;
11) to assess, in all cases, the contribution of MRLs at the LOQ to the exposure in all exposure scenarios;
12) to recommend MRLs that do not pose an unacceptable risk to consumers, where possible, and advise risk managers on alternative options. Where relevant, EFSA should indicate whether the achievable LOQs are sufficiently protective for consumers;
13) to share its draft reasoned opinion for consultation with Member States (MSs) and EURLs before finalising it.

EFSA accepted the mandate and to deliver its assessment by finalising separate reasoned opinions for each of the substances included in this mandate, including azocyclotin and cyhexatin, by 22 May 2023.

[6] The first EFSA scientific report in preparation of CCPR was prepared in 2010.
[7] The first evaluations of import tolerances under Regulation (EC) No 396/2005 which fully entered into force on 1.9.2008.
[8] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.OJ L 353, 31.12.2008, p. 1.

Assessment

To address the complex Terms of Reference (ToRs), EFSA used the following approach:

- In Section 1 (Regulatory background information on azocyclotin and cyhexatin), information on classification of the active substance under CLP regulation and on endocrine properties is reported (addressing ToR 10).
- In Section 2.1 (Nature of residues and residue definitions), a screening of the quality of residue definitions is reported (addressing ToR 8).
- In Section 2.2 (Analytical methods for MRLs enforcement), information on analytical methods for MRLs enforcement provided by the EURLs on the LOQs achievable during routine residues analysis is reported (ToR 4). In addition, EFSA summarised the information on the analytical methods assessed previously by EFSA and/or JMPR.
- In Section 2.3 (Existing MRLs), information on the origin of the current MRLs is reported in tabular format (ToR 1). In the same section, information provided by MSs on good agricultural practices (GAPs) authorised in third countries and previously evaluated in view of setting import tolerances can be found (ToR 2). This information, together with information on existing CXLs, is used to derive possible fall-back MRLs (ToR 3) that are also reported in the table if available.
- In Section 3 (Toxicological reference values), the quality of the TRVs set in the EU and by JMPR are assessed (ToR 7).
- In Section 4 (Consumer risk assessment), an indicative screening of the chronic and acute consumer exposure is presented (ToRs 5 and 6). The dietary exposure assessment is performed as requested in ToR 5 (a) and (b). This section also addresses ToR 11 (contribution of MRLs at the LOQ to the total exposure) and ToR 9 (comparison of the dietary exposure with the TRVs derived at EU and JMPR level). However, noting that following the experts' meeting on mammalian toxicology EFSA does not support the EU TRVs currently in place.
- In the Conclusions and recommendations section, EFSA presents the MRL proposals that are unlikely to pose an unacceptable risk to consumers, where possible, and the ones for which further consideration is required (ToR 12).

EFSA has based its assessment on the following documents:

- the Draft Assessment Reports (DAR) (Italy, 2008a,b);
- the Reports and Evaluations of the JMPR (FAO, 2005a,b);
- the reports of the Codex Committee on Pesticide residues (CCPR, 2006);

As requested in the ToR 2, Member States were invited to submit by 18 October 2022 the GAPs that are authorised in third countries and already evaluated at national level, in the format of specific GAP forms, as well as the supporting residue data, in the format of an evaluation report. In the framework of this consultation seven Member States (CZ, DE, ES, FR, IT, NL and SE) provided feedback regarding azocyclotin and cyhexatin and notified that no import tolerances were in place. The EU Reference Laboratories (EURLs) were also consulted (ToR 4) to provide an evaluation report on the availability of analytical methods for enforcement and the LOQs achievable during routine analysis in plants and animal commodities. The **EURLs report on analytical methods** (EURLs, 2022) submitted during the collection of data is considered as main supporting document to this reasoned opinion and, thus, made publicly available. In addition, an expert consultation in mammalian toxicology was conducted in January 2023; the **peer review meeting report TC 97** (EFSA, 2023a) is also considered as main supporting document.

On the basis of the data submitted by the MSs, the EURLs, the data available in the Joint Meeting on Pesticide residues (JMPR) Evaluation reports and taking into account the screening of the available toxicological data with regards to their completeness and quality according to the current standards, EFSA prepared a draft reasoned opinion, which was circulated to Member States and EURLs for consultation via a written procedure in March 2023. Comments received by 4 April 2023 were considered during the finalisation of this reasoned opinion (ToR 13).

Further supporting document to this reasoned opinion is the **Member States consultation report** (EFSA, 2023b). The exposure calculations for all crops reported in the framework of this review performed using the EFSA Pesticide Residues Intake Model (**PRIMo**) are also key supporting documents made publicly available as background document to this reasoned opinion.

1. Regulatory background information on azocyclotin and cyhexatin

The key events concerning the regulatory history of azocyclotin and cyhexatin, the background information, together with the relevant published documents are summarised in Table 1.

Table 1: Background information

Process	Status	Comments, references
Approval status	Not approved	Decision on non-inclusion of azocyclotin and cyhexatin in Annex I of Council Directive 91/414/EEC by Decision 2008/296/EC[(a)]
EFSA conclusion available	No	–
MRL review performed	No	–
EU MRL applications or other EU assessments	Yes, see comments	Implementation of CXLs adopted by CAC 2006 following discussion in CCPR 38 (2006) (i.e. CXLs for oranges, apples and wine grapes). These CXL values were included in Regulation (EC) 149/2008[(b)] and are the only MRL above the LOQ kept in Regulation (EU) 899/2012[(c)]
Classification under CLP Regulation	See comments	Azocyclotin: Acute Tox. 3*, H301 'toxic if swallowed' Skin Irrit. 2, H315 'causes skin irritation' Eye Dam. 1, H318 'causes serious eye damage' Acute Tox. 2*, H330 'fatal if inhaled' STOT SE 3, H335 'may cause respiratory irritation' (CLP00[(d)]) Cyhexatin: Acute Tox. 4*, H302 'harmful if swallowed' Acute Tox. 4*, H312 'harmful in contact with skin' Acute Tox. 4*, H332 'harmful if inhaled' (CLP00/ATP01[(e)])
Endocrine effects of a.s.	Not assessed	ED assessment according to ECHA and EFSA guidance (ECHA and EFSA, 2018) and scientific criteria (Commission Regulation (EC) No 2018/605[(f)]) have not been performed.

a.s: active substance; MRL: maximum residue limit; CXL: Codex maximum residue limit; CCPR: Codex Committee on Pesticide Residues; CAC: Codex Alimentarius Commission; CLP: classification, labelling and packaging; ED: endocrine disruptor; ECHA: European chemicals agency; ATP: 'adaptation to technical progress' list.

*: Indicates a minimum classification that must be classified in a more severe hazard category in the event that further information is available which shows that the hazard(s) meet the criteria for classification in the more severe category (see Annex VI, section 1,2,1 of CLP Regulation).

(a): Commission Decision 2008/296/EC of 4 April 2008 concerning the non-inclusion of azocyclotin, cyhexatin and thidiazuron in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing those substances. C(2008) 1187). OJ L 101, 11.4.2008, p. 9–10.

(b): Commission Regulation (EU) No 149/2008 of 29 January 2008 amending Regulation (EC) No 396/2005 of the European Parliament and of the Council by the establishing Annexes II, III and IV setting maximum residue levels for products covered by Annex I thereto. OJ L 58, 1.3.2008, p. 1–398.

(c): Commission Regulation (EU) No 899/2012 of 21 September 2012 amending Annexes II and III to Regulation (EC) No 396/2005 of the European Parliament and of the Council as regards maximum residue levels for acephate, alachlor, anilazine, azocyclotin, benfuracarb, butylate, captafol, carbaryl, carbofuran, carbosulfan, chlorfenapyr, chlorthal-dimethyl, chlorthiamid, cyhexatin, diazinon, dichlobenil, dicofol, dimethipin, diniconazole, disulfoton, fenitrothion, flufenzin, furathiocarb, hexaconazole, lactofen, mepronil, methamidophos, methoprene, monocrotophos, monuron, oxycarboxin, oxydemeton-methyl, parathion-methyl, phorate, phosalone, procymidone, profenofos, propachlor, quinclorac, quintozene, tolylfluanid, trichlorfon, tridemorph and trifluralin in or on certain products and amending that Regulation by establishing Annex V listing default values. OJ L 273, 6.10.2012, p. 1–75.

(d): Annex VI of Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC and amending Regulation (EC) No 1907/2006. OJ L 353, 31.12.2008, p. 1–1355.

(e): Commission Regulation (EC) No 790/2009 of 10 August 2009 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures. OJ L 235, 5.9.2009, p. 1–439.

(f): Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. OJ L 101, 20.4.2018, p. 33–36.

2. Residue definitions and existing EU MRLs

2.1. Nature of residues and residue definitions

As requested in point 8 of the ToR, EFSA summarised in this section the information used to derive the residue definitions for plant and animal products. Table 2 covers the studies submitted in the framework of the EU evaluation for inclusion in Annex I to Directive 91/414/EEC and studies that were submitted to JMPR in the framework of the setting of CXLs.

Table 2: Available metabolism studies.

Primary crops	Crop groups	Crop(s)	Application(s)	Sampling (DAT)	Comment/Source
	Fruit crops	Apple	Direct appl. to the surface of individual apples, 1 × 30 g a.s./hL	0, 7, 14, 21	[cyclohexyl-UL- ^{14}C]azocyclotin (FAO, 2005a,b; Italy, 2008a)
			Foliar (spray appl.), 1 × 3.8 kg a.s./ha	14	[^{119}Sn-Cyhexatin] (FAO, 2005a,b; Italy, 2008a,b)
		Grapes	Foliar (spray appl.), 1 × 0.3 kg a.s./ha	10, 28	[U-^{14}C]-Cyhexatin (FAO, 2005a,b; Italy, 2008a,b)
	Root crops	–	–	–	–
	Leafy crops	–	–	–	–
	Cereals/grass	–	–	–	–
	Pulses/oilseeds	–	–	–	–
Livestock	**Animal**		**Dose**	**Duration (days)**	**Comment/Source**
	Laying hen		100 mg/kg in the feed	4	[^{119}Sn-Cyhexatin] (FAO, 2005a,b; Italy, 2008a,b)
	Ruminant, cow		0.5 mg/kg bw/day	5	[cyclohexyl-UL-^{14}C]azocyclotin (FAO, 2005a,b; Italy, 2008a)
	Ruminant, goat		100 mg/kg in the feed	4	[^{119}Sn-Cyhexatin] (FAO, 2005a,b; Italy, 2008a,b)
	Pigs		–	–	Study not required as metabolism in rat and ruminant was found to be similar (FAO, 2005a,b; Italy, 2008a,b).

a.s.: active substance; DAT: days after treatment; bw: body weight.

Metabolism studies on apple (with cyhexatin and azocyclotin) and grapes (with cyhexatin) were assessed in the framework of the EU evaluation (Italy, 2008a,b) and by JMPR (FAO, 2005a,b). These studies conducted with azocyclotin and cyhexatin have shown that cyhexatin was the major compound to be found. The metabolites cyclohexylhydroxostannane (MCTA) and dicyclohexyloxostannane (DCTO) were found in lesser amounts (MCTA was found up to 14% of total radioactive residue (TRR), in apple peel and DTCO was found up to 14.8% TRR on grape surface) and were not considered of toxicological concern. Consequently, JMPR proposed to set the residue definitions for azocyclotin and cyhexatin, both for enforcement and risk assessment, as the sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b). Initially, in the framework of the EU evaluation, the following residue definitions were proposed both for enforcement and risk assessment: sum of azocyclotin and cyhexatin, expressed as cyhexatin for azocyclotin and cyhexatin for cyhexatin (Italy, 2008a,b). However, finally as the EU did not express reservation in the CCPR 38/CAC 28 in 2006, the same residue definitions as the ones proposed by JMPR were adopted in Regulation (EC) No 396/2005. The metabolism of the two active substances was investigated in one group only and no studies are available for root crops, leafy crops, cereals, and pulses, therefore the residue definitions should be applicable to fruit crops only. Nevertheless, the uses under consideration (see Table 5) are covered by the available plant metabolism studies.

The nature of cyhexatin and azocyclotin residues in livestock was investigated and assessed in the framework of the EU evaluation (Italy, 2008a,b) and by JMPR (FAO, 2005a,b). In the metabolism studies conducted in cows (azocyclotin), goats (cyhexatin) and laying hens (cyhexatin), cyhexatin was the major

compound to be found. The metabolites MCTA and DCTO were found in lesser amount (DCTO was found up to 30% TRR in hen tissues and MCTA up to 33% TRR in cow fat) and were not considered of toxicological concern. Consequently, it was proposed to set the residue definitions as the sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b). Although the log P_{ow} of cyhexatin is high (6.1 at pH 7), since metabolism studies conducted in cows, goats and hens indicated that cyhexatin does not concentrate in fat, JMPR concluded that the residues of cyhexatin were not fat soluble. The conclusions of the EU evaluation, based on the same studies, are in line with JMPR proposals.

Table 3 summarises the residue definitions derived at EU level and by JMPR. The EU residue definitions for enforcement are the ones set in Regulation (EC) No 396/2005. EU residue definitions for risk assessment were proposed in the framework of the EU evaluation. The same residue definitions for enforcement and risk assessment were derived by the JMPR (FAO, 2005a,b).

Table 3: Residue definitions derived at EU level and by JMPR

Type of residue definition (RD)	Commodity group	EU residue definition	JMPR residue definitions
RD for enforcement	Plant products	Reg. (EC) 396/2005: sum of azocyclotin and cyhexatin, expressed as cyhexatin. RMS proposal (Italy, 2008a,b), but not peer-reviewed: Azocyclotin: Sum of azocyclotin and cyhexatin, expressed as cyhexatin Cyhexatin: Cyhexatin	Sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b)
	Animal products	Reg. (EC) 396/2005: sum of azocyclotin and cyhexatin, expressed as cyhexatin. RMS proposal (Italy, 2008a,b), but not peer-reviewed: Azocyclotin: Sum of azocyclotin and cyhexatin, expressed as cyhexatin Cyhexatin: Cyhexatin	Sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b)
RD for risk assessment	Plant products	RMS proposal (Italy, 2008a,b), but not peer-reviewed: Azocyclotin: Sum of azocyclotin and cyhexatin, expressed as cyhexatin Cyhexatin: Cyhexatin	Sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b)
	Animal products	RMS proposal (Italy, 2008a,b), but not peer-reviewed: Azocyclotin: Sum of azocyclotin and cyhexatin, expressed as cyhexatin Cyhexatin: Cyhexatin	Sum of azocyclotin and cyhexatin, expressed as cyhexatin (FAO, 2005a,b)
Comments: The residue definitions for plant and animal products set in Reg. (EC) 396/2005 are identical with the ones proposed in the framework of JMPR assessments.			

2.2. Analytical methods for MRLs enforcement

Analytical methods for the determination of azocyclotin and cyhexatin residues were assessed in the framework of their assessment for inclusion in Annex I to Directive 91/414/EEC (Italy, 2008a,b). Analytical methods are available to enforce residues of azocyclotin and cyhexatin in high acid commodities with an LOQ of 0.01 mg/kg. Since the residue analysis method uses derivatisation, residues of azocyclotin and cyhexatin cannot be differentiated. No methods were reported to enforce azocyclotin and cyhexatin residues in high water, high oil and dry commodities.

Cyhexatin and azocyclotin residues can be enforced in food of animal origin with an LOQ of 0.1 mg/kg in muscle and liver (Italy, 2008a,b).

Analytical methods for the determination of azocyclotin and cyhexatin residues were also assessed in the framework of JMPR evaluation (FAO, 2005a,b). Analytical methods are available to enforce residues of azocyclotin and cyhexatin in high water and high acid commodities with an LOQ of 0.01 mg/kg, in dry commodities with an LOQ of 0.02 mg/kg (orange dry pulp) and 0.05 mg/kg (apple pomace dry) and in high oil commodities with an LOQ of 0.1 mg/kg. No methods were reported to monitor azocyclotin and cyhexatin residues in animal commodities.

During the data collection, the EURLs provided information on a QuEChERS single-residue analytical method using liquid chromatography with tandem mass spectrometry (LC–MS/MS) technique, with an LOQ of 0.01 mg/kg for the routine analysis of cyhexatin in high water and high acid commodities and using gas chromatography with tandem mass spectrometry (GC–MS/MS) with an LOQ of 0.01 mg/kg for the routine analysis of cyhexatin in dry commodities. No data were provided regarding the possible enforcement of cyhexatin in high oil content and animal commodities. Based on the general analytical behaviour of cyhexatin in other commodities, it is assumed that an LOQ of 0.02 mg/kg would be achievable for high oil commodities. Based on the general behaviour of cyhexatin in other commodities and of fentin and fenbutatin oxide in commodities of animal origin, it is assumed that, in all main commodities of animal origin except animal fat, cyhexatin can be monitored with a default LOQ of 0.01 mg/kg. An LOQ of 0.02 mg/kg for animal fat is deemed achievable (EURLs, 2022).

Experiments by the EURLs showed that cyhexatin and azocyclotin could not be distinguished analytically. Based on various tests with azocyclotin it is concluded that validation data for azocyclotin can be transferred to cyhexatin and vice versa. A conversion factor of 0.883 would need to be applied to express azocyclotin concentrations into cyhexatin (to account for the different molecular weights of azocyclotin and cyhexatin (EURLs, 2022).

It is concluded that analytical methods are available or presumed by EURLs to be achievable for all commodities under assessment. Table 4 provides an overview of the analytical methods available and their respective LOQs.

Table 4: Analytical methods available

Commodity group		Analytical method available	LOQ (mg/kg)	Source
Plant commodities	High water	Yes (GC-FPD)	0.01	FAO (2005a,b)
		Yes (QuEChERS method with LC–MS/MS)	0.01	EURLs (2022)
	High oil	Yes (GC-FPD)	0.1	FAO (2005a,b)
		–	0.02[(a)]	EURLs (2022)
	High acid content	Yes (GC-FPD)	0.01	FAO (2005a,b)
		Yes (GC-FPD)	0.01	Italy (2008a,b)
		Yes (QuEChERS method with LC–MS/MS)	0.01	EURLs (2022)
	Dry	Yes (GC-FPD)	0.02 (orange dry pulp) 0.05 (apple pomace dry)	FAO (2005a,b)
		Yes (QuEChERS method with GC–MS/MS)	0.01	EURLs (2022)
Animal commodities	Muscle	Yes (HPLC–MS/MS)	0.1	Italy (2008a,b)
		–	0.01[(b)]	EURLs (2022)
	Kidney	–	0.01[(b)]	EURLs (2022)
	Liver	Yes (HPLC–MS/MS)	0.1	Italy (2008a,b)
		–	0.01[(b)]	EURLs (2022)
	Fat	–	0.02[(b)]	EURLs (2022)
	Milk	–	0.01[(b)]	EURLs (2022)
	Eggs	–	0.01[(b)]	EURLs (2022)

LOQ: limit of quantification; GC-FPD: gas chromatography with flame photometric detector; GC–MS/MS: gas chromatography with tandem mass spectrometry; LC–MS/MS: liquid chromatography with tandem mass spectrometry; QuEChERS: Quick, Easy, Cheap, Effective, Rugged and Safe (analytical method).

(a): Although no validation data are available for this specific commodity within the EURLs, it is assumed that the reported LOQ would be achievable based on the general behaviour of cyhexatin in other commodities.

(b): Although no validation data are available for this specific commodity within the EURLs, it is assumed that the reported LOQ would be achievable based on the general behaviour of cyhexatin, fentin and fenbutatin in other commodities.

2.3. Existing MRLs

The EU MRLs for azocyclotin and cyhexatin are established in Annex II of Regulation (EC) No 396/2005. For a number of food products, CXLs have been taken over in the EU legislation. It should be noted that in the framework of the current review, Member States did not notify import tolerances in place.

EFSA reported in Table 5, the existing EU MRLs set above the LOQ for the respective crops, including information on the source of the MRLs together with the relevant GAPs and the references to the assessment where the MRL proposal was derived. In response to ToR 1 which requests to provide an analysis whether the existing EU MRL, the CXL or the import tolerance established for a crop is sufficiently substantiated, EFSA applied the following criteria:

A CXL is considered substantiated if:

- it is still in place (CXL has not been withdrawn from the Codex system);
- the CXL is sufficiently supported by data;
- the enforcement residue definition is identical with the EU residue definition.

An import tolerance is considered substantiated if:

- the GAP in the country of origin is still authorised;
- the import tolerance is sufficiently supported by data;
- the MRL in the country of origin is established at a level corresponding to the EU MRL (taking into account the potential difference in the RDs);
- in case the residue definition in the country of origin is different, the import tolerance is substantiated if sufficient information is available to derive an MRL for the EU RD.

An existing EU MRLs is considered not substantiated if:

- it is based on a previously authorised EU use;
- it is based on a previous CXL that has been revoked/withdrawn;
- it is based on an import tolerance that is no longer relevant as the use in the country of origin is not confirmed.

In order to address ToRs 3, 5 and 6, in cases where the current CXLs or import tolerances are not sufficiently substantiated, information on possible fall-back GAPs and the associated fall-back MRLs should be reported in 5. In the last column of this table, additional considerations relevant for taking a risk management decision can be also found.

Table 5: Background information on current MRLs for azocyclotin and cyhexatin established at a level above the LOQ

Commodity	Existing MRL (mg/kg)	Source of existing MRL	cGAP for existing MRL	Existing MRL substantiated? (Y/N)[a]	Fall-back GAP[b]	Fall-back MRL[b] (mg/kg)	Comment
Oranges	0.2	CXL (CAC, 2006)	Spain: foliar application, 0.25–0.31 kg ai/hL, PHI 15 days (FAO, 2005b) Brazil: foliar application, 0.025 kg a.s./hL, PHI 30 days (FAO, 2005b)	Y	n.r.	n.r.	The EU did not express a reservation in the CCPR 38/CAC in 2006. The CXL was implemented by Reg. (EU) 149/2008.
Apples	0.2	CXL (CAC, 2006)	Italy: 0.6 kg a.s./ha, PHI 30 days (FAO, 2005b) Spain: 0.036 kg a.s./ hL, PHI 28 days (FAO, 2005b)	tbd	–	–	The EU did not express a reservation in the CCPR 38/CAC in 2006. The CXL was implemented by Reg. (EU) 149/2008. Only European uses are reported in JMPR report (FAO, 2005a,b), therefore it is recommended that risk managers discuss whether this EU MRL is still substantiated.
Wine grapes	0.3	CXL (CAC, 2006)	Spain: 0.31 kg a.s./ha, PHI 30 days (FAO, 2005b)	tbd	–	–	The EU did not express a reservation in the CCPR 38/CAC in 2006. The CXL was implemented by Reg. (EU) 149/2008. Only European uses are reported in JMPR report (FAO, 2005a,b), therefore it is recommended that risk managers discuss whether this EU MRL is still substantiated.

MRL: maximum residue limit; CXL: Codex maximum residue limit; CAC: Codex Alimentarius Commission; CCPR: Codex committee on pesticide residues: GAP: good agricultural practice; cGAP: critical good agricultural practice; a.s.: active substance; PHI: preharvest interval; n.r.: not relevant; tbd: to be discussed.

(a): The criteria for deciding whether the existing MRL is sufficiently substantiated can be found in the paragraphs above the table. In the last column of this table, further explanations can be found why an existing MRL is considered not substantiated.

(b): Fall-back GAP and fall-back MRL are not relevant (n.r.), if the existing MRL is substantiated.

3. Toxicological reference values

EFSA was mandated to examine the available information in order to screen the quality of the TRVs set at EU level and of those established by the JMPR and to assess the completeness of the set of toxicological studies used to derive the TRVs according to the current standards (ToR 7).

Taking into account the quick conversion of azocyclotin to cyhexatin in aqueous solution, the RMS and JMPR considered appropriate to derive a group ADI and a group ARfD covering the toxicity of both compounds. The group TRVs for cyhexatin and azocyclotin reported in Table 6 were derived by the RMS Italy, in the DARs from 2006 (Italy, 2008a,b); the TRVs were not peer reviewed as the application was withdrawn. In 2005, the JMPR derived a group ADI and ARfD which can be found in Table 7; these values were retained by the EC for the derivation of MRLs.

The different ARfD and ADI values derived by the RMS and JMPR can be explained by a different interpretation of the same available studies and of the adversity of the same findings. The critical no observed adverse effect level (NOAEL) used by the JMPR to derive the ADI was considered as the lowest observable adverse effect level (LOAEL) by the RMS. Regarding the NOAELs relevant to derive the ARfD, the RMS also concluded on lower values compared to the JMPR assessment.

Table 6: Toxicological reference values (TRVs) proposed at EU level

TRV	Value	Reference	Comments
Group ADI	0.0014 mg/kg bw per day	Italy (2008a,b)	Based on the LOAEL of 0.43 mg/kg bw per day for increased incidence of bile duct hyperplasia and retinal atrophy observed in a 2-year study in rats conducted with cyhexatin and applying an increased UF of 300 to account for the use of a LOAEL as point of departure.
Group ARfD	0.007 mg/kg bw	Italy (2008a,b)	Based on an overall NOAEL of 0.7 mg/kg bw per day for acute effects (clinical signs, reduced body weight and embryotoxicity) in a multigeneration toxicity study in rats and a developmental toxicity study in rabbits and applying a standard UF of 100.

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; UF: uncertainty factor.

Table 7: Toxicological reference values (TRVs) set by the JMPR

TRV	Value	Reference	Comments
Group ADI	0.003 mg/kg bw per day	FAO (2005a,b)	Based on the NOAEL of 0.3 mg/kg bw per day for increased incidence of retinal atrophy in a 2-year rat study performed with cyhexatin and applying an UF of 100.
Group ARfD	0.02 mg/kg bw	FAO (2005a,b)	Based on the NOAEL of 2 mg/kg bw per day for embryotoxicity observed in developmental toxicity studies conducted with cyhexatin in rabbits and applying an UF of 100.

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight; UF: uncertainty factor.

EFSA screened the completeness and the quality of the toxicological studies that were used to derive the group TRVs by the RMS and the JMPR, focussing on the question as to whether the studies meet the current scientific standards. EFSA did not undertake a full review of the original studies; the basis of the TRVs derivation was scrutinised mainly based on the data reported in the original DARs (Italy, 2008a,b).

During this scrutiny, EFSA identified critical issues related to the available toxicological database which were discussed with Member State experts in mammalian toxicology during the Pesticides Peer Review Teleconference 97 in January 2023 (EFSA, 2023a).

The discussions with the Member State experts focussed on the following two critical points:

- the genotoxicity data set;
- the robustness of the available data to derive toxicological reference values, i.e. the ADI, the ARfD and respective UF.

The genotoxicity data packages for azocyclotin and cyhexatin contain studies assessing the three endpoints, i.e. gene mutation in bacterial and mammalian cells (*in vitro*), clastogenicity (*in vitro* and *in vivo*) and aneugenicity (*in vivo*).

For cyhexatin,[9] the studies for gene mutation showed negative (in bacterial and mammalian cells), positive and equivocal results (in mammalian cells). The *in vitro* clastogenicity study was positive with and without metabolic activation, while *in vivo* studies for clastogenicity and aneugenicity showed negative results. The studies were conducted in the 1980s and 1990s according to the OECD test guidelines in place at the time, or prior to their publication. One test guideline was deleted in the meantime, the *in vitro* unscheduled DNA synthesis assay TG 482 (OECD, 1986) that was considered relevant and reliable at the time of the evaluation in a weight of evidence assessment of the gene mutation potential of the test substance but is not considered relevant anymore.

Deviations with regards to current test guidelines (or concurrent test guidelines in case none were followed) could not be assessed, and the results of the *in vitro* studies could not be independently reviewed due to the lack of reporting details (e.g. tabulated results). With regards to *in vivo* studies (mammalian erythrocyte micronucleus tests in mice), proof of bone marrow exposure was shown when the test substance was administered by intraperitoneal injection (statistically significant reductions of the polychromatic/normochromatic erythrocytes (PCE/NCE) ratio compared to control animals), but not when the test substance was administered by oral gavage (no information on general toxicity induced by treatment, no change in the PCE/NCE ratio and plasma analysis was not performed), but taken together, the experts agreed that cyhexatin is unlikely to present clastogenicity or aneugenicity potential considering current standards (EFSA Scientific Committee, 2017).

It was noted that, according to the current scientific standards, if a substance is tested positive in an *in vitro* gene mutation test, a suitable *in vivo* follow-up test (e.g. *in vivo* Comet assay TG 489 (OECD, 2016) or transgenic rodent somatic and germ cell gene mutation assay TG 488 (OECD, 2022)) would be requested (EFSA Scientific Committee, 2011). The experts agreed that no conclusion can be reached on the genotoxic potential of cyhexatin due to the positive results observed *in vitro* in an AS52/XPRT mammalian cell forward gene mutation assay.

For azocyclotin,[10] the experts noted that the data base is poor when compared with current standards (old studies from the 1970s and 1980s, not performed according to GLP or OECD test guidelines, no report of the potential deviations with regards to OECD TG). Although the overall outcome of the various tests is reported as negative or equivocal, the quality of the available studies and reporting is not sufficient to conclude on the genotoxicity potential of azocyclotin according to current standards.

Overall, the genotoxicity data packages available for or cyhexatin or azocyclotin are not considered reliable. It is therefore not possible to conclude on their genotoxicity potential, in particular regarding the gene mutation potential of cyhexatin that presented positive results *in vitro*.

With regards to the toxicological data package needed to derive a group ADI and a group ARfD for cyhexatin and azocyclotin according to the current data requirements,[11] the experts identified major limitations and missing data. Due to the deficiencies listed below, the experts concluded that the derivation of toxicological reference values according to current scientific standards is not possible[12]:

- The genotoxic potential of cyhexatin and azocyclotin was found to be inconclusive.
- The assessment of the validity of the toxicological studies and reliability of their results is limited by the lack of details on the toxicological studies reported in the DARs (Italy, 2008a,b) (e.g. that do not allow to verify the compliance of these studies with the current or older versions of the test guidelines), and the unknown validity of the analytical methods used in feed, body fluids and tissues, air and any additional matrices used in support of the toxicity studies. These limitations imply, for instance, that it is not possible to understand the difference in NOAELs derived by the EU and the JMPR assessments, as is the case of the maternal and embryotoxicity NOAELs of the developmental and 2-generation reproductive toxicity studies in rats and developmental toxicity in rabbits (critical to the risk assessment).
- A search for published literature has not been conducted.

[9] See experts' consultation point 2.1 at the Pesticide Peer Review Teleconference 97 on cyhexatin (EFSA, 2023a).
[10] See experts' consultation point 2.1 at the Pesticide Peer Review Teleconference 97 on azocyclotin (EFSA, 2023a).
[11] Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, 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. OJ L 93, 3.4.2013, p. 1–84.
[12] See experts' consultation points 2.2 at the Pesticide Peer Review Teleconference 97 on cyhexatin and azocyclotin (EFSA, 2023a).

- The endocrine disruptive potential of azocyclotin and cyhexatin was not assessed according to the current ECHA/EFSA Guidance (ECHA and EFSA, 2018). It is expected that additional toxicological information would be needed to perform such an assessment.
- A comparative *in vitro* metabolism study performed on animal species used in pivotal studies and on human material is not available to determine the relevance of the toxicological animal data to humans and whether additional testing of potential unique human metabolites would be required.

The use of an additional uncertainty factor could not be established on the basis of deficiencies and uncertainties identified.

The JMPR values suffer from the same limitations as they appear to be based on the same toxicological studies, at least with regards to the genotoxicity data package.

It was concluded that the existing toxicological reference values proposed by the RMS or established by the JMPR cannot be confirmed for azocyclotin and cyhexatin since their genotoxicity potential is inconclusive, the data available are considered insufficient when compared to current standards, and uncertainty factors cannot be established.

Accordingly, considering that the ADI and ARfD used to establish the EU MRLs do not comply with the current scientific standards, EFSA would recommend their withdrawal.

4. Consumer risk assessment

In order to address ToR 5 (a) (Scenario 1), and (b) (Scenario 2) ToR 6 and ToR 11, EFSA calculated the chronic and acute dietary exposure, based on the current residue definition for risk assessment, i.e. sum of azocyclotin and cyhexatin, expressed as cyhexatin. Chronic and acute exposure calculations for all crops reported in the framework of this review were performed using revision 3.1 of the EFSA PRIMo (EFSA, 2018, 2019). All input values included in the exposure calculations are summarised in Appendix C.

As for some commodities, EFSA suggested two risk management options (i.e. for apples and wine grapes; see Table 5 and Appendix C), the following two sub-scenarios were calculated:

- **Scenario 1A**:
  - All CXLs and EU MRLs that are sufficiently substantiated or which were recommended for further risk management discussion (labelled as 'to be discussed' in Table 5) were considered for the exposure assessment, using the relevant risk assessment values for the current MRL. For the chronic exposure assessment, the calculation is based on the supervised trials median residue levels (STMR) derived for raw agricultural commodities (noting that for oranges, a peeling factor was applied). For the acute exposure assessment, the calculation is based on the highest residue levels (HR) expected in raw agricultural commodities. For oranges, the peeling factor was also included in the acute exposure assessment.
  - All other commodities where no GAP was reported in the framework of the MRL review were included in the calculation with the appropriate LOQ.
- **Scenario 1B**:
  - Same input values as in scenario 1A, except for the CXL/MRLs labelled as 'to be discussed' in Table 5, for which the appropriate LOQ was used, assuming that a risk management decision on the lowering of these MRLs would be taken.
- **Scenario 2:**
  - Like scenario 1A, but lowering all CXLs that were set before 2009 and never evaluated by EFSA to the appropriate LOQ.

The acute and chronic exposure calculations were compared to current EU TRVs (FAO, 2005a,b), noting that during the experts' meeting on mammalian toxicology held in January 2023, the experts concluded that these TRVs do not comply with the current scientific standards and therefore recommended to withdraw the existing EU TRVs (see Section 3). Thus, the risk assessment requested in ToR 5 and presented in this review is indicative only.

Screenshots of the report sheets of the indicative PRIMo calculations for scenarios 1A, 1B and 2 are presented in Appendix B.

In scenarios 1A, 1B and 2, the highest chronic exposure was calculated for NL toddler, representing respectively 51%, 44% and 42% of the ADI. The contribution of the MRLs set at the LOQ to the exposure represents 38% of the ADI for scenario 1A and 42% of the ADI for both scenarios 1B and scenario 2.

The highest acute exposure was calculated for apples in scenario 1A, representing 86% of the ARfD.

The toxicological assessment revealed deficiencies regarding the toxicological studies available for azocyclotin and cyhexatin (EFSA, 2023a) which do not fully comply with the current scientific standards. Considering the high level of uncertainty affecting the TRVs derived in 2005, EFSA did not confirm the previously derived TRVs. Therefore, the risk assessment cannot be finalised.

Conclusions and recommendations

The metabolism of azocyclotin and cyhexatin in plants and animals was previously investigated in the framework of the EU evaluation (Italy, 2008a,b) as well as by JMPR (FAO, 2005a,b). According to the results of the metabolism studies assessed, the residue definition for enforcement and risk assessment, both for plant and animal products, is the sum of azocyclotin and cyhexatin, expressed as cyhexatin.

Analytical methods are available for the enforcement of the proposed residue definition in high water and high acid content matrices with an LOQ of 0.01 mg/kg, in orange dry pulp with an LOQ of 0.02 mg/kg, in apple dry pomace with an LOQ of 0.05 mg/kg and in high oil content matrices with an LOQ of 0.1 mg/kg. Azocyclotin and cyhexatin residues can be enforced in food of animal origin with an LOQ of 0.1 mg/kg in muscle and liver. No method is available for the enforcement of residues in kidney, fat, milk and eggs. According to the EURLs, a QuEChERS multi-residue analytical method with an LOQ of 0.01 mg/kg for the routine analysis of azocyclotin and cyhexatin residues in high water, high acid and dry commodities. Based on the experience gained with these matrices, a default LOQ of 0.01 mg/kg in all commodities of animal origin except fat and a default LOQ of 0.02 mg/kg in fat and in high oil content matrices is also deemed achievable to monitor azocyclotin and cyhexatin residues.

The origin of all current MRLs set for azocyclotin and cyhexatin was investigated, and further risk management discussions are required to decide whether the existing EU MRL for apples and wine grapes should be maintained or lowered to the LOQ.

A screening of the quality of the group TRVs proposed by the RMS and of those established by the JMPR was performed, and the set of toxicological studies used to derive these TRVs was assessed according to the current standards. As critical issues were identified, a Member States experts' consultation took place. The experts concluded that the TRVs proposed by the RMS and derived by JMPR cannot be confirmed for azocyclotin and cyhexatin since the genotoxicity potential of either active substance was considered inconclusive, the data available were of insufficient reliability compared to current standards, and uncertainty factors could not be established. Accordingly, the ADI and ARfD used for the setting of MRLs do not comply with the current scientific standards. Therefore, EFSA recommends withdrawing these TRVs. The following data would be required to finalise the toxicological assessment which is a pre-requisite to derive robust TRVs:

- additional studies to conclude on the genotoxic potential of azocyclotin and cyhexatin;
- assessment of the validity of analytical methods used in feed, body fluids and tissues, air and any additional matrices used in support of the toxicological studies;
- literature search;
- additional toxicological data to perform an ED assessment;
- comparative *in vitro* metabolism study on animal species used in pivotal studies and on human material;
- full re-evaluation of the toxicological data package and reporting relevant details on the studies and the results in accordance with the current guidelines.

Chronic and acute exposure calculations were performed using revision 3.1 of PRIMo, considering commodities for which the existing EU MRLs were found to be sufficiently substantiated, while all CXLs/MRLs that could be no longer substantiated (upon risk managers' decision) were proposed to be lowered to the appropriate LOQ, as well as all other commodities for which no GAP was reported under this review. Comparing to the EU TRVs, no exceedances were observed, and the highest chronic exposure represented 51% of the ADI (NL toddler). The highest acute exposure amounted to 86% of the ARfD (apples). Nevertheless, EFSA emphasises that as the toxicological assessment revealed

deficiencies regarding the toxicological studies available for azocyclotin and cyhexatin and considering that EU TRVs do not meet the current scientific standards, the indicative risk assessment cannot be finalised, and results presented under the current review are indicative only.

Due to the deficiencies identified regarding the toxicological studies available for azocyclotin and cyhexatin, none of the existing EU MRLs listed in the table below (Table 8) are recommended for inclusion in Annex II to the Regulation. If a decision on the withdrawing of TRVs is taken, EFSA recommends that risk managers discuss whether all MRLs currently implemented in EU Regulation should be lowered to the respective LOQs.

Table 8: Summary table

Code[(a)]	Commodity	Existing MRL[(b)] (mg/kg)	Outcome of the review	
			MRL proposal (mg/kg)	Comment
Residue definition for enforcement (plants and animal products): Sum of azocyclotin and cyhexatin, expressed as cyhexatin				
0110020	Oranges	0.2	0.2 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards).
0130010	Apples	0.2	0.2 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as: – the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards) – this MRL was initially based on a CXL derived from European uses that are no longer authorised.
0151020	Wine grapes	0.3	0.3 or LOQ Further consideration by risk managers needed	The existing MRL is sufficiently substantiated. However, further risk management discussions are needed to decide whether the existing MRL needs to be lowered as: – the risk assessment could not be finalised, lacking robust TRVs for azocyclotin and cyhexatin (EFSA recommends withdrawing the previously derived EU TRV, as the toxicological database does not fully comply with the current scientific standards) – this MRL was initially based on a CXL derived from European uses that are no longer authorised.

MRL: maximum residue limit; CXL: Codex residue limit; LOQ: limit of quantification; TRV: toxicological reference value; GAP: good agricultural practice.
(a): Commodity code number according to Annex I of Regulation (EC) No 396/2005.
(b): MRL currently set under Regulation (EU) No 899/2012.

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Abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
a.s.	active substance
bw	body weight

CAC	Codex Alimentarius Commission
CCPR	Codex Committee on Pesticide Residues
cGAP	critical good agricultural practice
CLP	classification, labelling and packaging
CXL	Codex maximum residue limit
DAT	days after treatment
DAR	draft assessment report
DCTO	dicyclohexyloxostannane
ECHA	European Chemicals Agency
ED	endocrine disruptor
EURL	European Reference Laboratories
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
GC-FPD	gas chromatography with flame photometric detector
GC–MS/MS	gas chromatography with tandem mass spectrometry
HR	highest residue
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
MCTA	metabolites cyclohexylhydroxostannane
MRL	maximum residue level
MS	Member State
NOAEL	no observed adverse effect level
OJ	Official Journal of the European Union
OECD	Organisation for Economic Co-operation and Development
PeF	peeling factor
PHI	preharvest interval
PRIMo	(EFSA) Pesticide Residues Intake Model
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RD	residue definition
SCoPAFF	Standing Committee on Plants, Animals, Food and Feed (formerly: Standing Committee on the Food Chain and Animal Health; SCFCAH)
STMR	supervised trials median residue
ToR	Terms of Reference
TRR	total radioactive residue
TRV	toxicological reference values

Appendix A – Summary of the fall-back GAPs collected from Member States

Not applicable, as Member States reported no import tolerances for azocyclotin and cyhexatin.

Appendix B – Pesticide Residue Intake Model (PRIMo)

- PRIMo_(Sc. 1A)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Azocyclotin & Cyhexatin

LOQs (mg/kg) range from: 0.01 to: 0.05

Toxicological reference values

ADI (mg/kg bw per day):	0.003	ARfD (mg/kg bw):	0.02
Source of ADI:	JMPR	Source of ARfD:	JMPR
Year of evaluation:	2005	Year of evaluation:	2005

Input values

Details – chronic risk assessment | Supplementary results – chronic risk assessment

Details – acute risk assessment/children | Details - acute risk assessment/adults

Comments: **The EU TRVs established are not compliant with the current scientific standard. EFSA emphasises that the risk assessment presented under this review cannot be concluded and is indicative only.**
Scenario 1a: All commodities for which the existing MRL is sufficiently substantiated (and MRLs still to be discussed by risk managers) are included in the calculation. All Commodities for which no GAP was reported are lowered to the appropriate LOQ.

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity/ group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
TMDI/NEDI/IEDI calculation (based on average food consumption)	51%	NL toddler	1.54	20%	Milk: Cattle	11%	Apples	3%	Oranges	38%	13%
	33%	DE child	0.99	12%	Apples	7%	Milk: Cattle	5%	Oranges	16%	17%
	28%	NL child	0.84	8%	Milk: Cattle	6%	Apples	3%	Sugar beet roots	21%	7%
	23%	FR child 3 15 yr	0.70	8%	Milk: Cattle	4%	Oranges	2%	Apples	17%	7%
	23%	FR toddler 2 3 yr	0.68	10%	Milk: Cattle	3%	Apples	2%	Oranges	17%	5%
	22%	UK infant	0.67	13%	Milk: Cattle	2%	Apples	2%	Oranges	19%	3%
	20%	GEMS/Food G11	0.59	3%	Wine grapes	3%	Milk: Cattle	2%	Soyabeans	14%	5%
	19%	GEMS/Food G07	0.58	4%	Wine grapes	2%	Milk: Cattle	2%	Oranges	13%	7%
	18%	RO general	0.54	4%	Wine grapes	4%	Milk: Cattle	2%	Wheat	12%	6%
	18%	UK toddler	0.53	7%	Milk: Cattle	2%	Oranges	2%	Apples	14%	4%
	18%	DE women 14-50 yr	0.53	4%	Milk: Cattle	3%	Apples	2%	Oranges	11%	7%
	18%	GEMS/Food G08	0.53	3%	Wine grapes	2%	Milk: Cattle	1%	Wheat	13%	5%
	17%	GEMS/Food G15	0.52	3%	Wine grapes	2%	Milk: Cattle	2%	Wheat	13%	5%
	17%	DE general	0.51	4%	Milk: Cattle	2%	Apples	2%	Wine grapes	11%	6%
	16%	GEMS/Food G10	0.49	2%	Soyabeans	2%	Milk: Cattle	1%	Oranges	13%	3%
	16%	IE adult	0.47	3%	Wine grapes	1%	Milk: Cattle	1%	Oranges	10%	5%
	15%	ES child	0.46	4%	Milk: Cattle	3%	Oranges	1%	Wheat	12%	4%
	15%	DK child	0.46	4%	Milk: Cattle	2%	Apples	2%	Rye	13%	3%
	15%	GEMS/Food G06	0.46	2%	Wheat	1%	Tomatoes	1%	Oranges	13%	2%
	14%	PT general	0.43	7%	Wine grapes	2%	Potatoes	1%	Wheat	6%	8%
	14%	FR adult	0.41	6%	Wine grapes	1%	Milk: Cattle	0.8%	Apples	6%	8%
	14%	SE general	0.41	4%	Milk: Cattle	1%	Bovine: Muscle/meat	1%	Potatoes	12%	2%
	14%	NL general	0.41	3%	Milk: Cattle	2%	Wine grapes	1%	Apples	9%	4%
	13%	FI adult	0.40	9%	Coffee beans	0.8%	Wine grapes	0.6%	Apples	11%	2%
	11%	FR infant	0.34	6%	Milk: Cattle	2%	Apples	0.6%	Potatoes	9%	2%
	10%	ES adult	0.29	2%	Milk: Cattle	2%	Oranges	1%	Wine grapes	6%	3%
	8%	DK adult	0.25	3%	Wine grapes	2%	Milk: Cattle	1.0%	Apples	5%	4%
	8%	UK vegetarian	0.24	2%	Wine grapes	1%	Milk: Cattle	1%	Oranges	4%	4%
	8%	UK adult	0.24	3%	Wine grapes	1.0%	Milk: Cattle	0.7%	Oranges	4%	4%
	7%	FI 3 yr	0.20	2%	Potatoes	0.9%	Apples	0.4%	Bananas	6%	1%
	7%	LT adult	0.20	2%	Apples	1%	Milk: Cattle	1%	Potatoes	5%	2%
	7%	IT toddler	0.20	2%	Wheat	0.9%	Apples	0.6%	Oranges	5%	1%
	5%	FI 6 yr	0.16	1%	Potatoes	0.6%	Apples	0.4%	Cocoa beans	5%	0.8%
	5%	IT adult	0.15	1%	Wheat	0.8%	Apples	0.4%	Oranges	4%	1%
	5%	PL general	0.14	2%	Apples	1%	Potatoes	0.3%	Tomatoes	3%	2%
	3%	IE child	0.09	1%	Milk: Cattle	0.4%	Wheat	0.3%	Apples	3%	0.4%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health concern.

Acute risk assessment/children	Acute risk assessment/adults/general population
Details – acute risk assessment/children	Details – acute risk assessment/adults

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

Show results of IESTI calculation for all crops

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
86%	Apples	0.2 / 0.16	17
46%	Oranges	0.2 / 0.07	9.3
9%	Wine grapes	0.3 / 0.19	1.8
8%	Potatoes	0.01 / 0.01	1.5
8%	Melons	0.01 / 0.01	1.5
7%	Pears	0.01 / 0.01	1.4
6%	Milk: Cattle	0.01 / 0.01	1.2
6%	Watermelons	0.01 / 0.01	1.2
5%	Pineapples	0.01 / 0.01	1.0
5%	Avocados	0.02 / 0.02	1.0
5%	Bananas	0.01 / 0.01	0.97
5%	Peaches	0.01 / 0.01	0.95
4%	Mangoes	0.01 / 0.01	0.79
4%	Grapefruits	0.01 / 0.01	0.79
4%	Table grapes	0.01 / 0.01	0.73

Expand/collapse list

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
23%	Wine grapes	0.3 / 0.19	4.5
22%	Apples	0.2 / 0.16	4.5
11%	Oranges	0.2 / 0.07	2.1
2%	Head cabbages	0.01 / 0.01	0.42
2%	Watermelons	0.01 / 0.01	0.41
2%	Melons	0.01 / 0.01	0.39
2%	Milk: Cattle	0.01 / 0.01	0.39
2%	Swedes/rutabagas	0.01 / 0.01	0.34
2%	Table grapes	0.01 / 0.01	0.34
2%	Pears	0.01 / 0.01	0.31
2%	Avocados	0.02 / 0.02	0.30
1%	Potatoes	0.01 / 0.01	0.30
1%	Pineapples	0.01 / 0.01	0.30
1%	Yams	0.01 / 0.01	0.28
1%	Cucumbers	0.01 / 0.01	0.28

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
17%	Wine grapes / juice	0.3 / 0.08	3.5
13%	Oranges / juice	0.2 / 0.05	2.6
8%	Apples / juice	0.2 / 0.03	1.6
6%	Sugar beets (root) / sugar	0.01 / 0.12	1.1
5%	Potatoes / fried	0.01 / 0.01	0.93
4%	Pumpkins / boiled	0.01 / 0.01	0.89
4%	Witloofs / boiled	0.01 / 0.01	0.89
4%	Broccoli / boiled	0.01 / 0.01	0.79
3%	Cauliflowers / boiled	0.01 / 0.01	0.70
3%	Escaroles/broad-leaved endiv	0.01 / 0.01	0.66
3%	Potatoes / dried (flakes)	0.01 / 0.05	0.59
3%	Leeks / boiled	0.01 / 0.01	0.57
3%	Turnips / boiled	0.01 / 0.01	0.51
3%	Parsnips / boiled	0.01 / 0.01	0.51
3%	Sweet potatoes / boiled	0.01 / 0.01	0.50

Expand/collapse list

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
9%	Wine grapes / wine	0.3 / 0.19	1.8
8%	Wine grapes / juice	0.3 / 0.08	1.7
5%	Apples / juice	0.2 / 0.03	1.00
4%	Oranges / juice	0.2 / 0.05	0.76
3%	Pumpkins / boiled	0.01 / 0.01	0.55
2%	Sugar beets (root) / sugar	0.01 / 0.12	0.44
2%	Cauliflowers / boiled	0.01 / 0.01	0.42
2%	Beetroots / boiled	0.01 / 0.01	0.39
2%	Celeries / boiled	0.01 / 0.01	0.34
1%	Broccoli / boiled	0.01 / 0.01	0.24
1%	Coffee beans / extraction	0.05 / 0.01	0.24
1%	Courgettes / boiled	0.01 / 0.01	0.23
1%	Parsnips / boiled	0.01 / 0.01	0.21
1%	Kohlrabies / boiled	0.01 / 0.01	0.21
1%	Escaroles/broad-leaved	0.01 / 0.01	0.20

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health risk.
For processed commodities, no exceedance of the ARfD/ADI was identified.

- PRIMo_(Sc. 1B)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Azocyclotin & Cyhexatin

LOQs (mg/kg) range from: 0.01 to: 0.05

Toxicological reference values

ADI (mg/kg bw per day):	0.003	ARfD (mg/kg bw):	0.02
Source of ADI:	JMPR	Source of ARfD:	JMPR
Year of evaluation:	2005	Year of evaluation:	2005

Input values

Details – chronic risk assessment | Supplementary results – chronic risk assessment | Details – acute risk assessment/children | Details – acute risk assessment/adults

Comments: **The EU TRVs established are not compliant with the current scientific standard. EFSA emphasises that the risk assessment presented under this review cannot be concluded and is indicative only.**
Scenario 1b: All commodities for which the existing MRL is sufficiently substantiated are included in the calculation. MRLs still to be discussed by risk managers and all commodities for which no GAP was reported are lowered to the appropriate LOQ.

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

TMDI/NEDI/IEDI calculation (based on average food consumption)

Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity/ group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
44%	NL toddler	1.33	20%	Milk: Cattle	4%	Apples	3%	Oranges	42%	3%
25%	DE child	0.74	7%	Milk: Cattle	5%	Oranges	4%	Apples	20%	5%
24%	NL child	0.72	8%	Milk: Cattle	3%	Sugar beet roots	2%	Apples	23%	2%
21%	FR child 3 15 yr	0.64	8%	Milk: Cattle	4%	Oranges	2%	Wheat	18%	4%
21%	UK infant	0.64	13%	Milk: Cattle	2%	Oranges	1%	Potatoes	20%	2%
20%	FR toddler 2 3 yr	0.60	10%	Milk: Cattle	2%	Oranges	1%	Apples	18%	2%
17%	UK toddler	0.50	7%	Milk: Cattle	2%	Oranges	1%	Wheat	14%	2%
16%	GEMS/Food G11	0.48	3%	Milk: Cattle	2%	Soyabeans	1%	Potatoes	15%	0.9%
15%	GEMS/Food G07	0.45	2%	Milk: Cattle	2%	Oranges	1%	Wheat	14%	2%
15%	GEMS/Food G10	0.44	2%	Soyabeans	2%	Milk: Cattle	1%	Oranges	13%	1%
15%	ES child	0.44	4%	Milk: Cattle	3%	Oranges	1%	Wheat	12%	3%
14%	GEMS/Food G06	0.43	2%	Wheat	1%	Tomatoes	1%	Oranges	13%	1%
14%	GEMS/Food G08	0.43	2%	Milk: Cattle	1%	Wheat	1%	Soyabeans	14%	0.5%
14%	GEMS/Food G15	0.43	2%	Milk: Cattle	2%	Wheat	1%	Potatoes	13%	0.8%
14%	DE women 14-50 yr	0.42	4%	Milk: Cattle	2%	Oranges	2%	Sugar beet roots	12%	2%
14%	DK child	0.41	4%	Milk: Cattle	2%	Rye	1%	Wheat	14%	0.2%
13%	DE general	0.40	4%	Milk: Cattle	2%	Oranges	1%	Sugar beet roots	12%	2%
13%	SE general	0.39	4%	Milk: Cattle	1%	Bovine: Muscle/meat	1%	Potatoes	12%	0.9%
13%	RO general	0.39	4%	Milk: Cattle	2%	Wheat	1%	Potatoes	13%	0.3%
12%	IE adult	0.37	1%	Milk: Cattle	1%	Oranges	1%	Sweet potatoes	11%	1%
12%	FI adult	0.36	9%	Coffee beans	0.5%	Oranges	0.4%	Potatoes	12%	0.5%
11%	NL general	0.34	3%	Milk: Cattle	1%	Oranges	1.0%	Sugar beet roots	10%	1%
10%	FR infant	0.30	6%	Milk: Cattle	0.6%	Potatoes	0.6%	Apples	10%	0.3%
8%	ES adult	0.24	2%	Milk: Cattle	2%	Oranges	0.8%	Wheat	7%	2%
8%	FR adult	0.24	1%	Milk: Cattle	0.8%	Wine grapes	0.7%	Wheat	7%	0.7%
8%	PT general	0.23	2%	Potatoes	1%	Wheat	0.8%	Wine grapes	7%	0.7%
6%	FI 3 yr	0.18	2%	Potatoes	0.4%	Bananas	0.4%	Wheat	6%	0.2%
6%	IT toddler	0.18	2%	Wheat	0.6%	Oranges	0.5%	Other cereals	5%	0.6%
6%	UK vegetarian	0.17	1%	Milk: Cattle	1%	Oranges	0.7%	Wheat	5%	1%
6%	DK adult	0.17	2%	Milk: Cattle	0.4%	Potatoes	0.4%	Wheat	5%	0.2%
5%	LT adult	0.16	1%	Milk: Cattle	1%	Potatoes	0.6%	Apples	5%	0.1%
5%	UK adult	0.15	1.0%	Milk: Cattle	0.7%	Oranges	0.6%	Wheat	4%	0.7%
5%	FI 6 yr	0.15	1%	Potatoes	0.4%	Cocoa beans	0.3%	Wheat	5%	0.2%
4%	IT adult	0.13	1%	Wheat	0.4%	Oranges	0.4%	Tomatoes	4%	0.4%
3%	PL general	0.10	1%	Potatoes	0.7%	Apples	0.3%	Tomatoes	3%	0.0%
3%	IE child	0.08	1%	Milk: Cattle	0.4%	Wheat	0.2%	Potatoes	3%	0.1%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health concern.

Acute risk assessment/children	Acute risk assessment/adults/general population
Details – acute risk assessment/children	Details – acute risk assessment/adults

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

Show results of IESTI calculation for all crops

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
46%	Oranges	0.2 / 0.07	9.3
8%	Potatoes	0.01 / 0.01	1.5
8%	Melons	0.01 / 0.01	1.5
7%	Pears	0.01 / 0.01	1.4
6%	Milk: Cattle	0.01 / 0.01	1.2
6%	Watermelons	0.01 / 0.01	1.2
5%	Apples	0.01 / 0.01	1.1
5%	Pineapples	0.01 / 0.01	1.0
5%	Bananas	0.01 / 0.01	0.97
5%	Peaches	0.01 / 0.01	0.95
4%	Mangoes	0.01 / 0.01	0.79
4%	Grapefruits	0.01 / 0.01	0.79
4%	Table grapes	0.01 / 0.01	0.73
3%	Cucumbers	0.01 / 0.01	0.66
3%	Carrots	0.01 / 0.01	0.63

Expand/collapse list

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
11%	Oranges	0.2 / 0.07	2.1
2%	Head cabbages	0.01 / 0.01	0.42
2%	Watermelons	0.01 / 0.01	0.41
2%	Melons	0.01 / 0.01	0.39
2%	Milk: Cattle	0.01 / 0.01	0.39
2%	Swedes/rutabagas	0.01 / 0.01	0.34
2%	Table grapes	0.01 / 0.01	0.34
2%	Pears	0.01 / 0.01	0.31
1%	Potatoes	0.01 / 0.01	0.30
1%	Pineapples	0.01 / 0.01	0.30
1%	Yams	0.01 / 0.01	0.28
1%	Apples	0.01 / 0.01	0.28
1%	Cucumbers	0.01 / 0.01	0.28
1%	Aubergines/egg plants	0.01 / 0.01	0.27
1%	Mangoes	0.01 / 0.01	0.26

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
13%	Oranges / juice	0.2 / 0.05	2.6
6%	Sugar beets (root) / sugar	0.01 / 0.12	1.1
5%	Potatoes / fried	0.01 / 0.01	0.93
4%	Pumpkins / boiled	0.01 / 0.01	0.89
4%	Witloofs / boiled	0.01 / 0.01	0.89
4%	Broccoli / boiled	0.01 / 0.01	0.79
3%	Cauliflowers / boiled	0.01 / 0.01	0.70
3%	Escaroles/broad-leaved	0.01 / 0.01	0.66
3%	Potatoes / dried (flakes)	0.01 / 0.05	0.59
3%	Leeks / boiled	0.01 / 0.01	0.57
3%	Apples / juice	0.01 / 0.01	0.54
3%	Turnips / boiled	0.01 / 0.01	0.51
3%	Parsnips / boiled	0.01 / 0.01	0.51
3%	Sweet potatoes / boiled	0.01 / 0.01	0.50
2%	Florence fennels / boiled	0.01 / 0.01	0.45

Expand/collapse list

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
4%	Oranges / juice	0.2 / 0.05	0.76
3%	Pumpkins / boiled	0.01 / 0.01	0.55
2%	Sugar beets (root) / sugar	0.01 / 0.12	0.44
2%	Cauliflowers / boiled	0.01 / 0.01	0.42
2%	Beetroots / boiled	0.01 / 0.01	0.39
2%	Celeries / boiled	0.01 / 0.01	0.34
2%	Apples / juice	0.01 / 0.01	0.33
1%	Broccoli / boiled	0.01 / 0.01	0.24
1%	Coffee beans / extraction	0.05 / 0.01	0.24
1%	Courgettes / boiled	0.01 / 0.01	0.23
1%	Parsnips / boiled	0.01 / 0.01	0.21
1%	Kohlrabies / boiled	0.01 / 0.01	0.21
1%	Wine grapes / juice	0.01 / 0.01	0.21
1%	Escaroles/broad-leaved	0.01 / 0.01	0.20
1.0%	Florence fennels / boiled	0.01 / 0.01	0.19

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health risk.
For processed commodities, no exceedance of the ARfD/ADI was identified.

- PRIMo_(Sc. 2)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2019/03/19

Azocyclotin & Cyhexatin

LOQs (mg/kg) range from: 0.01 to: 0.05

Toxicological reference values

ADI (mg/kg bw per day):	0.003	ARfD (mg/kg bw):	0.02
Source of ADI:	JMPR	Source of ARfD:	JMPR
Year of evaluation:	2005	Year of evaluation:	2005

Input values

Details – chronic risk assessment | Supplementary results – chronic risk assessment | Details – acute risk assessment/children | Details – acute risk assessment/adults

Comments: **The EU TRVs established are not compliant with the current scientific standard. EFSA emphasises that the risk assessment presented under this review cannot be concluded and is indicative only.**
Scenario 2: All commodities for which the existing MRL was set before and including 2009 and all commodities for which no GAP was reported are lowered to the appropriate LOQ.

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

TMDI/NEDI/IEDI calculation (based on average food consumption)

Calculated exposure (% of ADI)	MS Diet	Exposure (µg/kg bw per day)	Highest contributor to MS diet (in % of ADI)	Commodity/ group of commodities	2nd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	3rd contributor to MS diet (in % of ADI)	Commodity/ group of commodities	Exposure resulting from: MRLs set at the LOQ (in % of ADI)	Exposure resulting from: commodities not under assessment (in % of ADI)
42%	NL toddler	1.27	20%	Milk: Cattle	4%	Apples	2%	Maize/corn	42%	
23%	NL child	0.69	8%	Milk: Cattle	3%	Sugar beet roots	2%	Apples	23%	
21%	DE child	0.64	7%	Milk: Cattle	4%	Apples	1%	Wheat	21%	
20%	UK infant	0.61	13%	Milk: Cattle	1%	Potatoes	0.9%	Wheat	20%	
19%	FR toddler 2 3 yr	0.56	10%	Milk: Cattle	1%	Apples	1%	Wheat	19%	
19%	FR child 3 15 yr	0.56	8%	Milk: Cattle	2%	Wheat	1%	Sugar beet roots	19%	
15%	GEMS/Food G11	0.46	3%	Milk: Cattle	2%	Soyabeans	1%	Potatoes	15%	
15%	UK toddler	0.45	7%	Milk: Cattle	1%	Wheat	1%	Potatoes	15%	
14%	GEMS/Food G07	0.42	2%	Milk: Cattle	1%	Wheat	1%	Potatoes	14%	
14%	GEMS/Food G08	0.42	2%	Milk: Cattle	1%	Wheat	1%	Soyabeans	14%	
14%	GEMS/Food G10	0.42	2%	Soyabeans	2%	Milk: Cattle	1%	Wheat	14%	
14%	GEMS/Food G15	0.41	2%	Milk: Cattle	2%	Wheat	1%	Potatoes	14%	
14%	DK child	0.41	4%	Milk: Cattle	2%	Rye	1%	Wheat	14%	
14%	GEMS/Food G06	0.41	2%	Wheat	1%	Tomatoes	0.8%	Milk: Cattle	14%	
13%	RO general	0.38	4%	Milk: Cattle	2%	Wheat	1%	Potatoes	13%	
13%	ES child	0.38	4%	Milk: Cattle	1%	Wheat	0.9%	Cocoa beans	13%	
12%	DE women 14-50 yr	0.37	4%	Milk: Cattle	2%	Sugar beet roots	0.9%	Apples	12%	
12%	SE general	0.37	4%	Milk: Cattle	1%	Bovine: Muscle/meat	1%	Potatoes	12%	
12%	DE general	0.36	4%	Milk: Cattle	1%	Sugar beet roots	0.8%	Apples	12%	
12%	FI adult	0.35	9%	Coffee beans	0.4%	Potatoes	0.2%	Rye	12%	
11%	IE adult	0.34	1%	Milk: Cattle	1%	Sweet potatoes	0.8%	Wheat	11%	
10%	NL general	0.31	3%	Milk: Cattle	1.0%	Sugar beet roots	0.8%	Potatoes	10%	
10%	FR infant	0.29	6%	Milk: Cattle	0.6%	Potatoes	0.6%	Apples	10%	
7%	FR adult	0.22	1%	Milk: Cattle	0.8%	Wine grapes	0.7%	Wheat	7%	
7%	PT general	0.22	2%	Potatoes	1%	Wheat	0.8%	Wine grapes	7%	
7%	ES adult	0.21	2%	Milk: Cattle	0.8%	Wheat	0.4%	Oranges	7%	
6%	FI 3 yr	0.18	2%	Potatoes	0.4%	Bananas	0.4%	Wheat	6%	
6%	IT toddler	0.17	2%	Wheat	0.5%	Other cereals	0.5%	Tomatoes	6%	
5%	DK adult	0.16	2%	Milk: Cattle	0.4%	Potatoes	0.4%	Wheat	5%	
5%	LT adult	0.16	1%	Milk: Cattle	1%	Potatoes	0.6%	Apples	5%	
5%	UK vegetarian	0.15	1%	Milk: Cattle	0.7%	Wheat	0.5%	Potatoes	5%	
5%	FI 6 yr	0.14	1%	Potatoes	0.4%	Cocoa beans	0.3%	Wheat	5%	
5%	UK adult	0.14	1.0%	Milk: Cattle	0.6%	Wheat	0.5%	Potatoes	5%	
4%	IT adult	0.12	1%	Wheat	0.4%	Tomatoes	0.3%	Apples	4%	
3%	PL general	0.10	1%	Potatoes	0.7%	Apples	0.3%	Tomatoes	3%	
3%	IE child	0.08	1%	Milk: Cattle	0.4%	Wheat	0.2%	Potatoes	3%	

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health concern.

Acute risk assessment/children	Acute risk assessment/adults/general population
Details – acute risk assessment/children	Details – acute risk assessment/adults

The acute risk assessment is based on the ARfD.
The calculation is based on the large portion of the most critical consumer group.

Show results of IESTI calculation for all crops

Unprocessed commodities

Results for children
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
8%	Potatoes	0.01 / 0.01	1.5
8%	Melons	0.01 / 0.01	1.5
7%	Pears	0.01 / 0.01	1.4
7%	Oranges	0.01 / 0.01	1.3
6%	Milk: Cattle	0.01 / 0.01	1.2
6%	Watermelons	0.01 / 0.01	1.2
5%	Apples	0.01 / 0.01	1.1
5%	Pineapples	0.01 / 0.01	1.0
5%	Bananas	0.01 / 0.01	0.97
5%	Peaches	0.01 / 0.01	0.95
4%	Mangoes	0.01 / 0.01	0.79
4%	Grapefruits	0.01 / 0.01	0.79
4%	Table grapes	0.01 / 0.01	0.73
3%	Cucumbers	0.01 / 0.01	0.66
3%	Carrots	0.01 / 0.01	0.63

Expand/collapse list

Results for adults
No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
2%	Head cabbages	0.01 / 0.01	0.42
2%	Watermelons	0.01 / 0.01	0.41
2%	Melons	0.01 / 0.01	0.39
2%	Milk: Cattle	0.01 / 0.01	0.39
2%	Swedes/rutabagas	0.01 / 0.01	0.34
2%	Table grapes	0.01 / 0.01	0.34
2%	Oranges	0.01 / 0.01	0.31
2%	Pears	0.01 / 0.01	0.31
1%	Potatoes	0.01 / 0.01	0.30
1%	Pineapples	0.01 / 0.01	0.30
1%	Yams	0.01 / 0.01	0.28
1%	Apples	0.01 / 0.01	0.28
1%	Cucumbers	0.01 / 0.01	0.28
1%	Aubergines/egg plants	0.01 / 0.01	0.27
1%	Mangoes	0.01 / 0.01	0.26

Total number of commodities exceeding the ARfD/ADI in children and adult diets (IESTI calculation)

Processed commodities

Results for children
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
6%	Sugar beets (root) / sugar	0.01 / 0.12	1.1
5%	Potatoes / fried	0.01 / 0.01	0.93
4%	Pumpkins / boiled	0.01 / 0.01	0.89
4%	Witloofs / boiled	0.01 / 0.01	0.89
4%	Broccoli / boiled	0.01 / 0.01	0.79
3%	Cauliflowers / boiled	0.01 / 0.01	0.70
3%	Escaroles/broad-leaved endiv	0.01 / 0.01	0.66
3%	Potatoes / dried (flakes)	0.01 / 0.05	0.59
3%	Leeks / boiled	0.01 / 0.01	0.57
3%	Apples / juice	0.01 / 0.01	0.54
3%	Oranges / juice	0.01 / 0.01	0.53
3%	Turnips / boiled	0.01 / 0.01	0.51
3%	Parsnips / boiled	0.01 / 0.01	0.51
3%	Sweet potatoes / boiled	0.01 / 0.01	0.50
2%	Florence fennels / boiled	0.01 / 0.01	0.45

Expand/collapse list

Results for adults
No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Processed commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
3%	Pumpkins / boiled	0.01 / 0.01	0.55
2%	Sugar beets (root) / sugar	0.01 / 0.12	0.44
2%	Cauliflowers / boiled	0.01 / 0.01	0.42
2%	Beetroots / boiled	0.01 / 0.01	0.39
2%	Celeries / boiled	0.01 / 0.01	0.34
2%	Apples / juice	0.01 / 0.01	0.33
1%	Broccoli / boiled	0.01 / 0.01	0.24
1%	Coffee beans / extraction	0.05 / 0.01	0.24
1%	Courgettes / boiled	0.01 / 0.01	0.23
1%	Parsnips / boiled	0.01 / 0.01	0.21
1%	Kohlrabies / boiled	0.01 / 0.01	0.21
1%	Wine grapes / juice	0.01 / 0.01	0.21
1%	Escaroles/broad-leaved	0.01 / 0.01	0.20
1.0%	Florence fennels / boiled	0.01 / 0.01	0.19
1.0%	Turnips / boiled	0.01 / 0.01	0.19

Conclusion:
No exceedance of the toxicological reference value was identified for any unprocessed commodity.
A short-term intake of residues of Azocyclotin & Cyhexatin is unlikely to present a public health risk.
For processed commodities, no exceedance of the ARfD/ADI was identified.

Appendix C – Input values for the exposure calculations

Commodity	Existing MRL (mg/kg)	Chronic risk assessment		Acute risk assessment	
		Input value (mg/kg)	Comment	Input value (mg/kg)	Comment
Risk assessment residue definition: Sum of azocyclotin and cyhexatin, expressed as cyhexatin					
Oranges	0.2	Scenario 1A et 1B: 0.035	STMR (CXL) × PeF (0.7)	0.07	HR (CXL) × PeF (0.7)
		Scenario 2: 0.01*	LOQ	Scenario 2: 0.01*	LOQ
Apples	0.2	Scenario 1A: 0.03	STMR (CXL)	Scenario 1A: 0.16	HR (CXL)
		Scenario 1B and 2: 0.01*	LOQ	Scenario 1B and 2: 0.01*	LOQ
Wine grapes	0.3	Scenario 1A: 0.08	STMR (CXL)	Scenario 1A: 0.19	HR (CXL)
		Scenario 1B and 2: 0.01*	LOQ	Scenario 1B and 2: 0.01*	LOQ
Other crops/ commodities	See Reg. (EU) No 899/ 2012	LOQ[(a)]			

STMR: median residue value; HR: highest residue; PeF: peeling factor; CXL: Codex maximum residue limit; LOQ: limit of quantification.

*: Indicates that the input value is set at the limit of quantification.

(a): LOQ of 0.02 mg/kg was applied to tree nuts oilseeds and oil fruits and herbs and edible flowers, and of 0.05 mg/kg to tea, coffee beans, herbal infusions, cocoa beans, carobs, hops and spices. A default LOQ of 0.01 mg/kg for all other commodities was applied.