REASONED OPINION

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

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Abstract

According to Article 12 of Regulation (EC) No 396/2005, EFSA has reviewed the maximum residue levels (MRLs) currently established at European level for the pesticide active substance. Although this active substance is not authorised within the European Union, MRLs were established by the Codex Alimentarius Commission (codex maximum residue limits; CXLs) and import tolerances were reported by Member States and the UK (including the supporting residues data). Considering that no toxicological reference values are currently established in Europe for novaluron because the peer review for the approval was terminated before an EFSA conclusion was issued, the toxicological profile of novaluron was also assessed, in order to be able to perform the consumer risk assessment in the framework of the art 12 MRL review. Based on the assessment of the available data, toxicological reference values were derived, and a consumer risk assessment was carried out for the existing CXLs and import tolerances. All CXLs and import tolerances were found to be supported by inadequate data and a possible chronic risk to consumers was identified. Hence, further consideration by risk managers is needed.

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

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Summary

Novaluron was evaluated in the framework of Directive 91/414/EEC with the United Kingdom as Rapporteur Member State (RMS). In 2012, a decision on the non-approval of the active substance was taken by Commission Implementing Decision 2012/187/EU after voluntary withdrawal of the support for the active substance by the applicant.

As the decision for non-approval of novaluron was taken 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.

In order to verify whether import tolerances may still be in place in some Member States, on 18 November 2019, EFSA initiated the collection of data for this active substance. In a first step, Member States and the UK were invited to submit by 18 December 2019 Good Agricultural Practices (GAPs) for import tolerances in a standardised way, in the format of specific GAP forms, allowing the designated rapporteur Member State Germany to identify the critical GAPs in the format of a specific GAP overview file. Subsequently, Member States and the UK were requested to provide residue data supporting the critical GAPs, within a period of 1 month, by 20 May 2020.

On the basis of all the data submitted by Member States, the UK and by the EU Reference Laboratories for Pesticides Residues (EURLs), EFSA asked the RMS to complete the Pesticide Residues Overview File (PROFile) and to prepare a supporting evaluation report. Considering that no toxicological reference values are currently established in Europe for novaluron because the 2011 peer review was terminated before an EFSA conclusion was issued, following withdrawal of the application for approval by the applicant, EFSA asked the RMS to update the evaluation report providing further toxicological data in order to be able to perform the consumer risk assessment in the framework of the art 12 MRL review.

The PROFile and evaluation report were provided by the RMS to EFSA on 15 December 2020. Subsequently, EFSA performed the completeness check of these documents with the RMS. The outcome of this exercise including the clarifications provided by the RMS, if any, was compiled in the completeness check report.

During the completeness check, EFSA asked the RMS to update the evaluation report including data on carcinogenicity/mutagenicity/reprotoxicity (CMR) and endocrine-disrupting (ED) properties. The additional toxicological data were included in a revised Evaluation report that was received by EFSA on 04 June 2021. Subsequently, Member States were invited to provide written comments on the toxicological data submitted by the RMS, within 30 July 2021.

On the basis of the feedback received by Member States and observations by EFSA on the toxicological assessment, an expert meeting was held on 15 September 2021. The conclusions of the expert meeting are reported in the Report on the pesticide peer review TC 60 - Novaluron (EFSA, 2021d).

Based on the information provided by the RMS, Member States, the UK and the EURLs, the written consultation on the assessment of the toxicological data and the outcome of the expert meeting on the toxicological data and taking into account the MRLs established by the Codex Alimentarius Commission, EFSA prepared in October 2021 a draft reasoned opinion, which was circulated to Member States and EURLs for consultation via a written procedure. Comments received by 5 November 2021 were considered during the finalisation of this reasoned opinion. The following conclusions are derived.

In the mammalian toxicology area, an acceptable daily intake (ADI) of 0.01 mg/kg body weight (bw) per day was derived from a 2-year oral toxicity study in rats and applying an uncertainty factor (UF) of 100. No acute reference dose (ARfD) was set and is not needed. Novaluron was considered unlikely to pose a risk to humans with regard to genotoxicity, carcinogenicity or toxicity to the reproduction, however the potential for novaluron to possess ED properties could not be concluded, in particular with regard to the androgen and steroidogenesis modalities. In addition, an ED assessment for non-EATS-mediated modalities (a concern exists for an ED action on metabolism) will remain inconclusive, lacking clearly established testing and mode of action (MoA) for non-EATS-mediated pathways. Uncertainties were identified in the toxicological assessment due to missing data linked to areas that could not be finalised (listed in the recommendations section), that are mainly referring to potential hazards of the active substance (e.g. neurotoxicity, immunotoxicity or phototoxicity), but did not require the use of an additional UF in deriving the ADI. However, this does not preclude that once these data are available, the setting of reference values would need to be reconsidered.

The metabolism of novaluron in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement and risk assessment can be proposed as novaluron. Considering the low water solubility of novaluron, studies investigating the effect of processing on the nature of residues are not required. Analytical methods are available for the enforcement of the proposed residue definition in high water and high acid content matrices at the limit of quantification (LOQ) of 0.01 mg/kg, however not fully validated. Analytical methods for high oil and dry commodities are missing.

According to the EURLs the LOQ of 0.01 mg/kg is achievable in the four main matrix groups of plant origin by using the QuEChERS method in routine analyses. According to the information provided by the EURLs, the analytical standard for novaluron is commercially available.

The available data are considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation. Since the available analytical methods are not fully validated and a trial is still missing to support the import tolerance on tomatoes, all derived MRLs are tentative.

Novaluron is authorised for use on crops that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance. The dietary burdens calculated for cattle, sheep and goat were found to exceed the trigger value of 0.1 mg/kg dry matter (DM).

The metabolism of novaluron residues in livestock was investigated in lactating goats and laying hens at dose rate covering the maximum dietary burdens calculated in this review. According to the results of these studies, the residue definition for enforcement and risk assessment in livestock commodities was proposed as novaluron only. The residue definition is fat soluble. An analytical method based on liquid chromatography with tandem mass spectrometry (LC–MS/MS) using one MS/MS transition only, with an LOQ of 0.1 mg/kg for fat, 0.05 mg/kg for liver/kidney and 0.02 mg/kg for milk/muscle, and confirmatory method is available. An analytical method using gas chromatography with electron capture detector (GC-ECD) with an LOQ of 0.01 in eggs is available but confirmatory data is missing. An independent laboratory validation (ILV) for all livestock matrices is missing. According to the EURLs, the LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses.

Livestock feeding studies on lactating cows were used to derive MRL and risk assessment values in milk and tissues of ruminants. Since an ILV is missing for the analytical methods in all animal matrices, the derived MRLs are tentative. MRLs for poultry and swine products are not required because these livestock are not expected to be exposed to significant levels of novaluron residues.

Chronic consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 3.1 of the EFSA PRIMo. The exposure values calculated were compared with the toxicological reference values for novaluron, derived in the framework of this assessment. The highest chronic exposure was calculated for the NL toddler and DE children, representing 135% and 103% of the ADI, respectively. The main contributor was apples (75% and 87% of the ADI, respectively). A second exposure calculation (scenario EU2) was therefore performed, excluding apples. According to the results of this second calculation, the highest chronic exposure declined to 61% of the ADI for the NL toddler.

Apart from the MRLs evaluated in the framework of this review, internationally recommended CXLs have also been established for novaluron. Additional calculations of the consumer exposure, considering these CXLs, were therefore carried out. The highest chronic exposure was calculated for the NL toddler and DE child, representing 191% and 130% of the ADI, respectively. A second exposure calculation was therefore performed, excluding the CXLs for apples and pears, identified among the main contributors of the chronic exposure. According to the results of this second calculation, the highest chronic exposure declined to 91% of the ADI for NL toddler.

Table of contents

Background

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

Novaluron was evaluated in the framework of Directive 91/414/EEC with the United Kingdom as Rapporteur Member State (RMS). Following the submission of an application for inclusion of novaluron in Annex I of Directive 91/414/EEC, Member States were given a possibility to grant provisional authorisation for plant protection products containing novaluron in accordance with Article 8(1) of Directive 91/414/EEC for a period of 3 years. According to Commission Decision 2009/579/EC[3] of 29 July 2009, the period to grant provisional authorisation of novaluron was extended until 29 July 2011. On 16 June 2011, additional information was requested from the applicant to support the application for the approval. On 29 February 2012, the applicant withdrew its application without providing additional information and in 2012 a decision on the non-approval of the active substance was taken by Commission Implementing Decision 2012/187/EU.[4]

Subsequently, no EFSA conclusion was finalised. Following non-approval of novaluron, 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[5]. It should be noted, however, that, in the framework of Regulation (EC) No 1107/2009, only a few representative uses are evaluated, whereas MRLs set out in Regulation (EC) No 396/2005 should accommodate all uses authorised within the European Union (EU), and uses authorised in third countries that have a significant impact on international trade. The information included in the assessment report prepared under Regulation (EC) No 1107/2009 is therefore insufficient for the assessment of all existing MRLs for a given active substance.

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

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

As the basis for the MRL review, on 18 November 2019 EFSA initiated the collection of data for this active substance. In a first step, Member States and the UK[6] were invited to submit by 18 December 2019 Good Agricultural Practices (GAPs) for import tolerances, in a standardised way, in the format of specific GAP forms. In the framework of this consultation, 10 Member States and the UK provided feedback on import tolerances of novaluron. Based on the GAP data submitted, the designated RMS Germany was asked to identify the critical GAPs to be further considered in the assessment, in the

[1] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

[2] Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market. OJ L 230, 19.8.1991, p. 1–32. Repealed by Regulation (EC) No 1107/2009.

[3] Commission Decision of 29 July 2009 allowing Member States to extend provisional authorisations granted for the new active substances acequinocyl, aminopyralid, ascorbic acid, benalaxyl-M, mandipropamid, novaluron, proquinazid, spirodiclofen and spiromesifen (notified under document number C(2009) 5582). OJ L 198, 30.7.2009, p. 80–81.

[4] Commission Implementing Decision of 4 April 2012 amending Decision 2001/861/EC as regards novaluron (notified under document C(2012) 2164). OJ L 101, 11.4.2012, p. 15–17.

[5] 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.

[6] The United Kingdom withdrew from EU on 1 February 2020. In accordance with the Agreement on the Withdrawal of the United Kingdom from the EU, and with the established transition period, the EU requirements on data reporting also apply to the United Kingdom data collected until 31 December 2020.

format of a specific GAP overview file. Subsequently, in a second step, Member States and the UK were requested to provide residue data supporting the critical GAPs by 20 May 2020.

On the basis of all the data submitted by Member States, the UK and the EU Reference Laboratories for Pesticides Residues (EURLs), EFSA asked Germany to complete the PROFile and to prepare a supporting evaluation report. Considering that no toxicological reference values are currently established in Europe for novaluron because the 2011 peer review was terminated before an EFSA conclusion was issued, EFSA asked the RMS to include in the evaluation report the assessment on the toxicological profile of novaluron, in order to be able to perform the consumer risk assessment in the framework of the art 12 MRL review. The PROFile and the supporting evaluation report were submitted to EFSA on 15 December 2020. Subsequently, EFSA performed the completeness check of these documents with the RMS. The outcome of this exercise including the clarifications provided by the RMS, if any, was compiled in the completeness check report.

During the completeness check, EFSA asked the RMS to update the evaluation report including data on carcinogenicity/mutagenicity/reprotoxicity (CMR) and endocrine-disrupting (ED) properties. The additional toxicological data were included in a revised Evaluation report that was received by EFSA on 4 June 2021. Subsequently, Member States were invited to provide written comments on the toxicological data submitted by the RMS, within 30 July 2021.

On the basis of the feedback received by Member States and observations by EFSA on the toxicological assessment, an expert meeting was held on 15 September 2021. The conclusions of the expert meeting are reported in Report on the pesticide peer review TC 60 - Novaluron (EFSA, 2021d).

Based on the information provided by the RMS, Member States, the UK and the EURLs, the written consultation on the assessment of the toxicological data, the outcome of the expert consultation and taking into account the MRLs established by the Codex Alimentarius Commission (CAC) (i.e. codex maximum residue limit; CXLs), EFSA prepared in October 2021 a draft reasoned opinion, which was circulated to Member States and EURLs for commenting via a written procedure. All comments received by 5 November 2021 were considered by EFSA during the finalisation of the reasoned opinion.

The **evaluation report** submitted by the RMS (Germany, 2020), taking into account also the information provided by Member States and the UK during the collection of data and the **EURLs report on analytical methods** (EURLs, 2020) 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, 2021a), the **Member States consultation report on the draft reasoned opinion** (EFSA, 2021b), the **Member States Consultation Report on toxicological data** (EFSA, 2021c) and the **Report on the pesticide peer review TC 60 - Novaluron** (EFSA, 2021d). These reports are developed to address all issues raised in the course of the review, from the initial completeness check to the reasoned opinion. Furthermore, the exposure calculations for all crops reported in the framework of this review performed using the EFSA Pesticide Residues Intake Model (**PRIMo**) and the **PROFile** as well as the **GAP overview file** listing all authorised uses and import tolerances 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

Novaluron is the ISO common name for (*RS*)-1-3-chloro-4-[1,1,2-trifluoro-2-trifluoromethoxyethoxy) phenyl]-3-(2,6-difluorobenzoyl)urea (IUPAC).

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

The EU MRLs for novaluron are established in Annexes IIIA of Regulation (EC) No 396/2005. CXLs for novaluron were also established by the CAC. An overview of the MRL changes that occurred since the entry into force of the Regulation mentioned above is provided below (Table 1).

Table 1: Overview of the MRL changes since the entry into force of Regulation (EC) No 396/2005

Procedure	Legal implementation	Remarks
MRL application	Reg. (EU) No 813/2011(1)	Import tolerance for cranberries (EFSA, 2010)
Implementation of CAC 2011	Reg. (EU) No 441/2012(2)	CXLs for apricots, cherries (sweet), peaches, plums, strawberries, blueberries, sweet peppers/bell peppers, aubergines/eggplants, cucumbers, courgettes, cucurbits with inedible peel, broccoli, red mustards, chards/beet leaves, beans with and without pods, dry beans, sugar cane and commodities of animal origin were implemented in the EU legislation. Due to different extrapolation rules MRL finally implemented in the EU legislation for stone fruits, cucurbits with edible peel, fruiting vegetables other than cucurbits and brassica deviate from the CXLs implemented by the CAC (EFSA, 2011).

(1): Commission Regulation (EU) No 813/2011 of 11 August 2011 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 acequinocyl, emamectin benzoate, ethametsulfuron-methyl, flubendiamide, fludioxonil, kresoxim-methyl, methoxyfenozide, novaluron, thiacloprid and trifloxystrobin in or on certain products Text with EEA relevance. OJ L 208, 13.8.2011, p. 23–79.

(2): Commission Regulation (EU) No 441/2012 of 24 May 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 bifenazate, bifenthrin, boscalid, cadusafos, chlorantraniliprole, chlorothalonil, clothianidin, cyproconazole, deltamethrin, dicamba, difenoconazole, dinocap, etoxazole, fenpyroximate, flubendiamide, fludioxonil, glyphosate, metalaxyl-M, meptyldinocap, novaluron, thiamethoxam, and triazophos in or on certain products Text with EEA relevance. OJ L 135, 25.5.2012, p. 4–56.

For the purpose of this MRL review, all the uses of novaluron in third countries as submitted by the Member States and the UK during the GAP collection, have been reported by the RMS in the GAP overview file. The critical GAPs identified in the GAP overview file were then summarised in the PROFile and considered in the assessment. The details of the authorised critical GAPs for novaluron considered in this MRL review are given in Appendix A.

Assessment

EFSA has based its assessment on the following documents:

- the PROFile submitted by the RMS;
- the evaluation report accompanying the PROFile and respective Appendix C.2 containing the original summaries of the toxicological studies submitted by the applicant reviewed and commented by the EMS DE (Germany, 2020);
- Report on the MS Consultation on toxicological data (EFSA, 2021c);
- the report on the pesticide peer review TC 60 -Novaluron (EFSA, 2021d)
- residue and analytical methods sections from the draft assessment report (DAR) prepared under Council Directive 91/414/EEC (The United Kingdom, 2005);
- the Joint Meeting on Pesticide residues (JMPR) Evaluation report (FAO, 2005, 2010a,b);
- the previous reasoned opinion on novaluron (EFSA, 2010).

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[7] 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.

[7] Commissiossn 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. Mammalian toxicology

Novaluron was discussed at the Pesticide Peer Review Experts' Meeting TC60 in September 2021.

It is noted that, as this assessment refers to import tolerances, there is no information on the technical specification of either the tested material or the product actually used outside Europe, or information on the toxicological relevance of the potential impurities to which consumers may be exposed to. However, three studies on impurities (two Ames tests and an acute oral toxicity study in rat) were submitted that did not raise a concern. Analytical methods used in the toxicity studies (particularly relevant to the repeated-dose studies), a residue definition for monitoring purposes in body fluids and tissues as well as an analytical method to analyse novaluron (or its metabolites) in body fluids and tissues were not provided.

Following oral administration, novaluron is poorly absorbed (ca. 6–9% when administered at the low dose level of 2 mg/kg body weight (bw) and radiolabelled on its chlorophenyl moiety), based on urinary and biliary excretion. A higher absorption of 21% was observed when the substance was radiolabelled on its difluorophenyl moiety but this value could be an overestimate since it is suspected that a cleavage of the molecule will occur in the gastrointestinal tract prior to absorption that may alter the absorption. The active substance is widely distributed, with greatest levels found in fat, liver, kidneys, adrenals, pancreas and mesenteric lymph nodes. A potential for bioaccumulation was shown by prolonged plasma half-lives and increased area under the curve (AUC) for plasma by a factor of 5 after 168 h in the repeated dose groups compared to single administration. Once absorbed, the substance was extensively metabolised, mainly by the cleavage of the urea bridge between the chlorophenyl and difluorophenyl moieties, resulting in a major metabolite, 275-158 I (2,6-difluorobenzoic acid), retrieved up to 10.6–12% of the administered dose in urine; it was hypothesised that its counter chlorophenyl aniline moiety, 275-309 I (3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline) may not have been absorbed to the same extent as it accounted for less than 1% of the administered dose. This latter metabolite could however also be considered a major metabolite in rats when the amount retrieved in urine is corrected by the oral absorption of 6–9%. In contrast, the major part of the administered dose (more than 80%) was excreted via faeces as unchanged parent.

Novaluron is of low acute oral and inhalation toxicity; no data were provided on acute dermal toxicity, skin and eye irritation, skin sensitisation and phototoxicity as this data were considered not relevant to import tolerances.

Short-term administration to mice, rats and dogs produced typical signs of regenerative haemolytic anaemia, being erythrocytes a clear target of novaluron. Dose-related increase in body weight gain (without increase in food consumption), increase in triglycerides, total cholesterol and serum glucose were also recurrently observed in these three species indicating pathological changes in fat metabolism. The overall short-term no observed adverse effect level (NOAEL) is 0.7 mg/kg bw per day for increased body weight gain, increased triglycerides at the lowest observed adverse effect level (LOAEL) of 3.5 mg/kg bw per day and signs indicative of haemolytic anaemia (reduced erythrocytes, haematocrit and haemoglobin, hemosiderin pigments in spleen, increased spleen weight, extramedullary haematopoiesis) observed at higher dose levels (LOAELs of other studies) from the 90-day oral toxicity studies in rats.

Novaluron is unlikely to be genotoxic based on the available *in vitro* genotoxicity studies: Ames test, cytogenetic test in human lymphocytes, mouse lymphoma mutagenesis assay and *in vitro* micronucleus test.[8] It is noted that a justification for waiving photomutagenicity testing was not provided.

Upon long-term exposure, the same target on erythrocytes was observed in rats and mice. No test substance-related carcinogenic effects were observed in either species. The critical NOAEL was established at 1.1 mg/kg bw per day for haematological changes indicative of haemolytic anaemia and liver toxicity (periacinar hepatocytic hypertrophy) observed at 30.6 mg/kg bw per day in the 2-year study in rats.

In the two-generation reproductive toxicity study in rats, the dose levels used were too high to derive NOAELs. A LOAEL of 74 mg/kg bw per day was identified for increase body weight and spleen weight in adults, increased body weight, spleen and liver weight, as well as delayed preputial separation in offspring's; reproductive toxicity at this dose level was reported as reduced epididymal

[8] For full details on the expert's discussion, please refer to the experts' consultation point 2.5 of the Report on the pesticide peer review TC 60 - Novaluron (EFSA, 2021d) and the Member States consultation report on the toxicological data of novaluron (EFSA, 2021c).

sperm and changes in oestrus cycle. Developmental toxicity in rats consisted of reduced implantations, increased post-implantation loss and reduced corpora lutea concomitant with maternal increases in body weight. In rabbits, increased incomplete ossification (5th sternebrae) was observed at a dose showing an apparent lack of maternal toxicity with a NOAEL at 100 mg/kg bw per day; maternal toxicity in this study included reduced body weight gain with a NOAEL at 300 mg/kg bw per day.

No sign of a specific neurotoxic potential was observed in an acute neurotoxicity study in rats up to the limit dose of 2000 mg/kg bw. Repeated dose neurotoxicity was not investigated, either in the short-term toxicity studies or with a specific repeated-dose neurotoxicity study. Immunotoxicity was also not addressed. Regarding the ED potential of novaluron, thyroid (T) modality, it was agreed that the criteria are not met for the T-modality in a sufficiently investigated data set. For the oestrogen, androgen and steroidogenesis (EAS) modalities, it was also agreed that the data set is incomplete for the AS modalities. Some EAS-mediated endpoints were affected (spermiogenesis and oestrus cycle), but these were not considered sufficient to indicate that an AS-mediated pattern of adversity exists. No additional studies are necessary to investigate the E modality since the ToxCast E-model is negative, but additional information is needed to complete the AS modalities. According to scenario 2a(iii), further data should be generated:

- OECD TG 458 (AR STTA assay)
- OECD TG 456 (H295R steroidogenesis assay)
- OPPTS 890.1200 (Aromatase assay)

In case of negative results in the three studies, a Hershberger assay (OECD TG 441) should be performed. In case of positive results in one of the studies: OECD TG 443 or OECD TG 416 (2001) is requested. Uncertainties exist on the potential for novaluron to affect non-EATS-mediated endocrine pathways, in particular a concern exists for an endocrine disrupting action on metabolism (e.g. metabolic syndrome), this is mainly based on the recurrent observation in the data set of an increase in body weight gain in the absence of an increase in food consumption, and increases in cholesterol, triglycerides and glucose levels. However, in line with the ECHA/EFSA guidance on the identification of endocrine disrupters (ECHA and EFSA, 2018) and lacking clear testing and mode of action (MoA) for non-EATS-mediated pathways, the ED assessment for non-EATS pathway will remain inconclusive.[9]

Medical data on manufacturing plant personnel are missing. A report of pesticides poisoning incident in farm workers exposed to off-target drift of a pesticide mixture could not determine which ingredient, or if several in concert, were responsible for the symptoms observed (low to moderate severity illness with neurological, gastrointestinal, ocular and respiratory symptoms).

The acceptable daily intake (ADI) was established at 0.01 mg/kg bw per day, based on the NOAEL of 1.1 mg/kg bw per day for haematological findings indicative of haemolytic anaemia and liver toxicity observed in the 2-year oral toxicity study in rats and applying an uncertainty factor (UF) of 100. The setting of an acute reference dose (ARfD) was not considered necessary as the sole potential acute effect observed in the dossier (methaemoglobinaemia) did not reach a level of toxicological relevance in either dogs or rats upon (sub)acute exposure; accordingly, no ARfD was derived.

No toxicological information has been submitted on metabolites and is not needed for the current assessment (see residues sections). It is however noted that metabolite 275-158 I (2,6-difluorobenzoic acid) identified in the metabolism study on lactating goat (see Section 3.1) and metabolite 275-309 I (3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline) are considered major rat metabolites and the toxicological reference values of novaluron may apply to them.

Although not under EFSA's remit,[10] considerations for classification were provided in the Evaluation Report (ER) and no proposal for classification were agreed, in particular with regard to the carcinogenic, mutagenic or reproductive toxicity hazards.

A search for open literature was performed by the RMS in July 2020, nine studies were retained as relevant after detailed assessment and included in the dossier.

A list of the relevant end points for the active substance is provided in Appendix B.1.

[9] For full details on the expert's discussion, please refer to the experts' consultation point 2.9 of the Report on the pesticide peer review TC 60 - Novaluron (EFSA, 2021d).

[10] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with 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, 1–1355.

2. Residues in plants

2.1. Nature of residues and methods of analysis in plants

2.1.1. Nature of residues in primary crops

The primary metabolism of novaluron labelled on the chlorophenyl or difluorophenyl label was studied in representative crops of fruits (apples), leafy vegetables (cabbages), root and tuber vegetables (potatoes) and pulses and oilseeds (cotton), following foliar applications (United Kingdom, 2005; Germany, 2020).

An overview of all available metabolism studies is reported in Appendix B.2.1.1.

Either two or three applications were made to apple trees at a rate of 2.5–2.7 mg/tree per application (equivalent to 50–80 g a.s./ha). The applications were made 110, 90, and 60 days (for the three applications only) before harvest. Novaluron comprised more than 90% total radioactive residue (TRR) in all fruit samples at all applications and sampling intervals. No other component individually represented more than 1.3% of the TRR (0.001 mg/kg) in fruits or greater than 1.7% TRR (0.024 mg/kg) in leaves. All other compounds were below the limit of detection of 0.001–0.03 mg eq/kg (1–5% TRR).

Cotton plants were treated at an application rate equivalent to 50 g a.s./ha in two different regimes: regime (1) consisted of two applications, 14 days apart with a 90 day preharvest interval (PHI); regime (2) consisted of two applications which were 14 days apart with a 30-day PHI (Germany, 2020). Samples from plants treated according to regime 1 were taken for analysis after each application and at 60 and 30 days before normal harvest. Samples from plants treated according to regime 2 were taken for analysis after each application event and at normal harvest. The maximum TRR on undelinted seed was 0.005 mg/kg for both regimes. Unchanged novaluron constituted 88–95% of the TRR.

Two applications were made on potatoes growing in outdoor pots at a rate of 91–100 g a.s./ha. Whole plant samples were taken after each application and at 22, 10 and 0 days before harvest. For both radiolabels, the TRR on tubers at all intervals was < 0.001 mg eq/kg. At harvest (29 days after the second application), the TRR on plants was 9.9 mg eq/kg and 5.9 mg eq/kg, for both labels, respectively. Unchanged novaluron made up 97% of the TRR in both labels.

Following two applications of 30–45 g a.s./ha on cabbage, residues were 0.23–0.35 mg/kg (application done at 6 weeks PHI) and 0.32–0.45 mg eq/kg (application done at 2 weeks PHI). About 96–100% of the TRR on cabbage heads at harvest was identified as unchanged novaluron.

It is noted that the application rates used in the studies were underdosed when compared to the cGAPs under review (0.2 and 0.25N for the uses on apples and cotton, respectively). Nevertheless, since no significant metabolism or degradation of novaluron was observed under the various conditions tested in any of the crop groups and at all PHI intervals (more than 90% of the TRR in all crops was recovered as novaluron) the available metabolism studies are considered sufficient to cover the authorised uses under assessment.

2.1.2. Nature of residues in rotational crops

Novaluron is not approved in the EU and the only uses under assessment are import tolerances, thus consideration on rotational crops is not required. However, a confined rotational crop study was assessed by the RMS (Germany, 2020). Spinach, turnip and wheat were sown in soil 30 days after application of novaluron at approximately 100 g a.s./ha and sampled at various stages up to harvest. All crop samples showed total residues of less than 0.01 mg eq/kg, thus further characterisation was not performed.

2.1.3. Nature of residues in processed commodities

Hydrolysis studies investigating the effect of processing on the nature of residues are not required for active substances with a water solubility below 0.01 mg/L, such as novaluron which has a water solubility of 0.003 mg/L. Therefore, further investigation on the nature of the residues in processed commodities is not required.

It is noted that in a previous EFSA reasoned opinion on novaluron (EFSA, 2010), in the DAR (The United Kingdom, 2005) and in the Evaluation report (Germany, 2020) a hydrolysis study was reported. Nevertheless, for the reason above, results from this study were not considered reliable and were not considered further in the assessment.

2.1.4. Methods of analysis in plants

An analytical method for the detection of novaluron in plant commodities with high water content using gas chromatography with electron capture detector (GC-ECD) is reported in the DAR (The United Kingdom, 2005), and an additional method based on liquid chromatography with tandem mass spectrometry (LC–MS/MS) (Germany, 2020), but these studies were not peer-reviewed. The limit of quantification (LOQ) of both methods is 0.01 mg/kg. For the second method, an independent laboratory validation (ILV) was performed but is not acceptable because validation of the primary method and the ILV were performed in the same test facility. Hence, it can be concluded that an analytical method for plant commodities with high water content is available, using LC–MS/MS with an LOQ of 0.01 mg/kg. Although not needed, since LC–MS/MS is highly specific, a confirmatory method based on GC-ECD is available. However, an ILV is missing (data gap).

An analytical method for commodities with high acid content based on GC-ECD is available with an LOQ of 0.01 mg/kg (Germany, 2020), however, a confirmatory method and an ILV are missing (data gap).

Analytical methods for enforcement of novaluron in high oil and dry commodities are missing (data gap).

According to the EURLs an LOQ of 0.01 mg/kg is achievable in all four main plant matrix groups during routine analysis (EURLs, 2020).

An overview of all available methods is reported in Appendix B.2.1.1.

2.1.5. Stability of residues in plants

The storage stability of novaluron was investigated in the DAR (The United Kingdom, 2005), in a previous MRL assessment (EFSA, 2010) and in studies submitted under this review (Germany, 2020). The storage stability of novaluron was investigated in high water content matrices (The United Kingdom, 2005, Germany, 2020), high acid content matrices (EFSA, 2010; Germany, 2020) and in high oil content matrices and orange processed commodities (Germany, 2020). An overview of all available studies is reported in Appendix B.2.1.2.

Novaluron is stable in high-water content commodities when stored frozen for either up to six months (apples, broccoli, cabbage) or twelve months (tomatoes) at −18°C (The United Kingdom, 2005; Germany, 2020). In blueberries novaluron is stable for up to 141 days at −38 and −0.2°C (EFSA, 2010). Storage data produced as part of a study on the magnitude of the residue of novaluron in cotton, demonstrated that novaluron residues were stable over 5 months in cotton seeds and gin trash at −20°C (Germany, 2020).

2.1.6. Proposed residue definitions

The metabolism of novaluron was similar in all crops assessed. The metabolism study in rotational crops did not allow for a further characterisation as residues were below 0.01 mg/kg. Considering the low water solubility of novaluron, studies investigating the effect of processing on the nature of residues are not required.

As the parent compound was found to be a sufficient marker in fruits, leafy vegetables, roots and pulses and oilseeds, the residue definition for enforcement is proposed as novaluron only. The same residue definition is applicable to processed commodities. Since novaluron is not approved in the European Union and the only uses under assessment are import tolerances a specific residue definition is not required for rotational crops.

An analytical method for the enforcement of the proposed residue definition at the LOQ of 0.01 mg/kg in high water content matrices is available, but an ILV is missing (Germany, 2020). An analytical method for commodities with high acid content is available with an LOQ of 0.01 mg/kg, however, a confirmatory method and an ILV are missing (Germany, 2020). Analytical methods for high oil and dry commodities are missing.

According to the EURLs, the LOQ of 0.01 is achievable in the four main matrix groups by using the QuEChERS method in routine analyses (EURLs, 2020).

For risk assessment, the residue definition is proposed as novaluron for primary crops, rotational crops and processed commodities.

2.2. Magnitude of residues in plants

2.2.1. Magnitude of residues in primary crops

To assess the magnitude of novaluron residues resulting from the reported GAPs, EFSA considered all residue trials reported by the RMS in its evaluation report (Germany, 2020) as well as the residue trials evaluated in the framework of a previous MRL application (EFSA, 2010). An overview of the available residue trials is reported in Appendix B.2.2.1. All residue trial samples considered in this framework were stored in compliance with the conditions for which storage stability of residues was demonstrated. Decline of residues during storage of the trial samples is therefore not expected.

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

For all crops, available residue trials are sufficient to calculate (tentative) MRL and risk assessment values, taking note of the following considerations:

- Tomatoes: Although tentative MRL and risk assessment values can be derived from the import tolerance indoor GAP limited data set, 1 additional trial compliant with this GAP is still required.

2.2.2. Magnitude of residues in rotational crops

There were no studies investigating the magnitude of residues in rotational crops available for this review. Since novaluron is not approved in the European Union and the only uses under assessment are import tolerances only, these are not required.

2.2.3. Magnitude of residues in processed commodities

The effect of industrial processing and/or household preparation was assessed on studies conducted on apples and tomatoes (Germany, 2020). An overview of all available processing studies is available in Appendix B.2.2.3. Robust processing factors (fully supported by data) could be derived for apple juice, apple wet and dry pomace, tomato canned and juice, while tentative processing factors (not fully supported by data) were derived for tomato paste, plums dried and cotton meal, hulls and refined oil.

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

2.2.4. Proposed MRLs

The available data are considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation. Considering the data gaps identified in the previous sections (fully validated analytical methods and a residue trial on tomatoes) all MRLs are tentative.

3. Residues in livestock

Novaluron is authorised for use on crops that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance (OECD, 2013), which has now also been agreed upon at European level. The input values for all relevant commodities are summarised in Appendix D. The dietary burdens calculated for cattle and sheep were found to exceed the trigger value of 0.1 mg/kg dry matter (DM). Behaviour of residues was therefore assessed in these groups of livestock.

3.1. Nature of residues and methods of analysis in livestock

The metabolism of novaluron residues in livestock was investigated in lactating goats (The United Kingdom, 2005; Germany, 2020) and laying hens (Germany, 2020) at dose rates covering the maximum dietary burdens calculated in this review. In the studies performed with goats novaluron was labelled on the difluorophenyl and chlorophenyl rings, whereas the study with hens was performed with the novaluron labelled on the difluorophenyl ring only. An overview of the available metabolism studies is reported in Appendix B.3.1.1.

In lactating goats, cleavage of the urea bridge in the molecule resulted in metabolite 275-158-I (2,6-difluorobenzoic acid) present at 5.1% TRR, 0.007 mg/kg in kidney and metabolite 275-352-I (1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]urea) present at 7.3% TRR, 0.025 mg/kg in liver. An unknown fraction, comprised of several sections was identified in tissues and milk. Novaluron was found largely unchanged in milk. Novaluron undergoes only minor metabolism in goats. A plateau in milk was not reached by the end of the study which indicates the possibility of residues accumulating in milk or edible fatty tissues.

In laying hens, residues detected in all tissues and eggs consisted primarily of unmetabolised novaluron. No further component of the residue was identified. The TRR was highest in fat tissues. The results of the study indicate that there was very little or no cleavage of the urea bridge in the novaluron structure, as undergoes only minor metabolism in hens.

An analytical method based on LC–MS/MS using one MS/MS transition only, with an LOQ of 0.1 mg/kg for fat, 0.05 mg/kg for liver/kidney and 0.02 mg/kg for milk/muscle was reported (Germany, 2020). An ILV is provided for muscle, milk and liver but is not acceptable because primary validation and ILV were performed in the same test facility. A second method reported in the DAR, validated for muscle, milk, eggs, fat, liver and kidney, based on GC-ECD with an LOQ of 0.01 mg/kg, can be used as confirmatory method for liver, kidney, milk and muscle and as a primary method for eggs.

Therefore, it can be concluded that a validated method for novaluron in milk, muscle, fat, liver and kidney, including a confirmatory method, is available. However, an ILV for all animal commodities as well as a confirmatory method for eggs are missing (data gap).

The EURLs reported that during routine analyses an LOQ is 0.01 mg/kg is achievable in muscle, liver, milk and egg.

No storage stability information was provided for ruminant commodities and storage intervals from collection to analysis were not reported (Germany, 2020). According to the study dates reported, all experimental work was completed however within 53 days of the first sacrifice. This seems to indicate that at least some of the matrices were analysed after storage of more than one month.

As the parent compound was found to be a sufficient marker in livestock commodities, the residue definition for enforcement is proposed as novaluron only. The residue definition is fat soluble (see also results of poultry feeding study reported in Section 3.2).

For risk assessment, parent is toxicologically relevant and thus should be considered in the consumer exposure. For what concerns the metabolites identified in liver and kidney, metabolite 275-158-I has the same toxicity as the parent, while there is no toxicological data available for metabolite 275-352-I (see Section 1). Nevertheless, the metabolism study was performed with 8–14 N rate when compared to the maximum dietary burden calculated in this MRL review. Thus, these metabolites would occur at levels way below 0.01 mg/kg, when considering the uses under assessment. Therefore, the residue for risk assessment is proposed as novaluron only and further investigation on the metabolites is not required under the current assessment. If further uses would lead to an increase of the dietary burden, further consideration of metabolites may be needed.

3.2. Magnitude of residues in livestock

Feeding studies were performed with lactating cows and laying hens (Germany, 2020). In the ruminant study, novaluron was administered using different dosing levels ranging from 0.088 to 0.88 mg as/kg bw/d (values based on day 1 body weight). The study performed on lactating cow was used to derive MRL and risk assessment values in milk and tissues of cattle and sheep. In this study, samples of tissues and milk were analysed for novaluron. Residues in milk plateaued between day-28 and day-39 depending on the dose group and when adjusting for milk yield of animals in feeding study (Germany, 2020. It is noted that storage intervals from collection to analysis were not reported, and no further storage stability information was provided for the various ruminant commodities (data gap). Therefore, all derived MRLs should be considered tentative only.

In the poultry study, novaluron was administered using different dosing levels ranging from 0.12 to 1.2 mg feed for 56/57 days. Residues in eggs plateaued around day 19. At 0.12 mg/kg feed for eight weeks mean residues in hens´ tissues were reported at 0.012 mg/kg for muscle, 0.3 mg/kg for fat and 0.05 mg/kg for eggs (Germany, 2020). The residues in tissues reflected the lipophilic nature of novaluron with muscle having the least amount of residue and fat the highest. Nevertheless, MRLs for poultry and swine products are not required because these livestock are not expected to be exposed to significant levels of novaluron residues.

4. Consumer risk assessment

In the framework of this review, only the uses of novaluron reported by the RMS in Appendix A were considered; however, the use of novaluron was previously also assessed by the JMPR (FAO, 2005, 2010a,b). The CXLs, resulting from these assessments by JMPR and adopted by the CAC, are now international recommendations that need to be considered by European risk managers when establishing MRLs. To facilitate consideration of these CXLs by risk managers, the consumer exposure was calculated both with and without consideration of the existing CXLs (see Appendices B.4.1 and B.4.2) Due to different extrapolation rules, the EU presented a reservation regarding the CXLs for Brassica (cole or cabbage) vegetables, head cabbage, flowerhead brassicas; fruiting vegetables other than cucurbits; fruiting vegetables, cucurbits; stone fruits (EFSA, 2011). Consequently, for some commodities (e.g. okra, head cabbages, flowerhead cabbages) the CXLs were finally not legally implemented in the EU Regulation (and are not considered further in this review), while for others, MRL values that were legally implemented in the EU regulation differed from the CXLs proposed by the JMPR, since these were derived from the residue trials assessed by the JMPR but using the EU approach to derive MRLs for individual crops and/or the EU extrapolation rules. This was the case for apricots, peaches, plums, tomatoes, aubergines, sweet peppers, cucumbers, courgettes and broccoli. Therefore, for these crops the STMR values were re-calculated based on the residue trials on the individual crops reported in the JMPR (FAO, 2010a,b) in line with the proposal made by EFSA in the preparation for the CCPR (EFSA, 2011) that lead to the MRLs currently implemented in the EU regulation. It is noted that when Codex MRLs were derived, the risk assessment was performed with the previous version of PRIMo, i.e. PRIMo rev. 2. For the CXLs that were legally implemented in the EU legislation, no intake concerns were identified (EFSA, 2011).

4.1. Consumer risk assessment without consideration of the existing CXLs

Chronic 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). Input values for the exposure calculations were derived in compliance with the decision tree reported in Appendix E. Hence, for those commodities 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 ARfD was not deemed necessary for this active substance.

The exposure values calculated were compared with the toxicological reference values for novaluron, derived in the present assessment and reported in section 1. The highest chronic exposure was calculated for the NL toddler and DE children, representing 135% and 103% of the ADI, respectively. The main contributor was apples (75% and 87% of the ADI, respectively). A second exposure calculation (scenario EU2) was therefore performed, excluding apples. According to the results of this second calculation, the highest chronic exposure declined to 61% of the ADI for the NL toddler.

Based on these calculations, a chronic risk to consumers was identified for the most critical GAP of novaluron on apples. Fall-back GAPs were not available for this crop thus no further refinements of the risk assessment were possible. For the remaining commodities, although uncertainties remain due to the data gaps identified in the previous sections, the indicative exposure calculation did not indicate a risk to consumers.

4.2. Consumer risk assessment with consideration of the existing CXLs

To include the CXLs in the calculations of the consumer exposure, CXLs were compared with the EU MRL proposals in compliance with Appendix E and all data relevant to the consumer exposure assessment have been collected from JMPR evaluations. An overview of the input values used for this exposure calculation is also provided in Appendix D.

Chronic and acute exposure calculations were also performed using revision 3.1 of the EFSA PRIMo and the exposure values calculated were compared with the toxicological reference values derived for novaluron. The highest chronic exposure was calculated for the NL toddler and DE child, representing 191% and 130% of the ADI, respectively. The main contributors for the NL toddler were milk (cattle),

apples and pears at 78%, 70% and 30%, respectively, while for DE child the main contributors were apples, milk (cattle) and cherries sweet at 81%, 26% and 8%, respectively. A second exposure calculation was therefore performed, excluding the CXLs for apples and pears. According to the results of this second calculation, the highest chronic exposure declined to 91% of the ADI for NL toddler.

Based on these calculations, EFSA concludes that the CXLs for novaluron are not of concern for European consumers, except for the CXLs on apples and pears where a potential risk to consumers was identified and no further refinements of the risk assessment were possible. For the remaining CXLs, although uncertainties remain due to the data gaps identified, the indicative exposure calculation did not indicate a risk to consumers.

Conclusions

In the mammalian toxicology area, an ADI of 0.01 mg/kg bw per day was derived from a 2-year oral toxicity study in rats and applying an UF of 100. No ARfD was set and is not needed. Novaluron was considered unlikely to pose a risk to humans with regard to genotoxicity, carcinogenicity or toxicity to the reproduction, however the potential for novaluron to possess endocrine disrupting properties could not be concluded, in particular with regard to the androgen and steroidogenesis modalities. In addition, an ED assessment for non-EATS-mediated modalities (a concern exists for an ED action on metabolism) will remain inconclusive, lacking clearly established testing and MoA for non-EATS-mediated pathways. Uncertainties were identified in the toxicological assessment due to missing data linked to areas that could not be finalised (listed in the recommendations below), that are mainly referring to potential hazards of the active substance (e.g. neurotoxicity, immunotoxicity or phototoxicity), but did not require the use of an additional UF in deriving the ADI. However, this does not preclude that once these data are available, the setting of reference values would need to be reconsidered.

The metabolism of novaluron in plant was investigated in primary and rotational crops. According to the results of the metabolism studies, the residue definition for enforcement and risk assessment can be proposed as novaluron. Considering the low water solubility of novaluron, studies investigating the effect of processing on the nature of residues are not required. Analytical methods are available for the enforcement of the proposed residue definition in high water and high acid content matrices at the LOQ of 0.01 mg/kg, however not fully validated. Analytical methods for high oil and dry commodities are missing.

According to the EURLs, the LOQ of 0.01 mg/kg is achievable in the four main matrix groups of plant origin by using the QuEChERS method in routine analyses. According to the information provided by the EURLs, the analytical standard for novaluron is commercially available.

The available data are considered sufficient to derive MRL proposals as well as risk assessment values for all commodities under evaluation. Since the available analytical methods are not fully validated and a trial is still missing to support the import tolerance on tomatoes, all derived MRLs are tentative.

Novaluron is authorised for use on crops that might be fed to livestock. Livestock dietary burden calculations were therefore performed for different groups of livestock according to OECD guidance. The dietary burdens calculated for cattle, sheep and goat were found to exceed the trigger value of 0.1 mg/kg DM.

The metabolism of novaluron residues in livestock was investigated in lactating goats and laying hens at dose rate covering the maximum dietary burdens calculated in this review. According to the results of these studies, the residue definition for enforcement and risk assessment in livestock commodities was proposed as novaluron only. The residue definition is fat soluble. An analytical method based on LC–MS/MS using one MS/MS transition only, with an LOQ of 0.1 mg/kg for fat, 0.05 mg/kg for liver/kidney and 0.02 mg/kg for milk/muscle, and confirmatory method is available. An analytical method using GC-ECD with an LOQ of 0.01 in eggs is available but confirmatory data is missing. An ILV for all livestock matrices is missing. According to the EURLs the LOQ of 0.01 mg/kg is achievable by using the QuEChERS method in routine analyses.

Livestock feeding studies on lactating cow were used to derive MRL and risk assessment values in milk and tissues of ruminants. Since an ILV is missing for the analytical methods in all animal matrices, the derived MRLs are tentative. MRLs for poultry and swine products are not required because these livestock are not expected to be exposed to significant levels of novaluron residues.

Chronic consumer exposure resulting from the authorised uses reported in the framework of this review was calculated using revision 3.1 of the EFSA PRIMo. The exposure values calculated were

compared with the toxicological reference values for novaluron, derived in the framework of this assessment. The highest chronic exposure was calculated for the NL toddler and DE children, representing 135% and 103% of the ADI, respectively. The main contributor was apples (75% and 87% of the ADI, respectively). A second exposure calculation (scenario EU2) was therefore performed, excluding apples. According to the results of this second calculation, the highest chronic exposure declined to 61% of the ADI for the NL toddler.

Apart from the MRLs evaluated in the framework of this review, internationally recommended CXLs have also been established for novaluron. Additional calculations of the consumer exposure, considering these CXLs, were therefore carried out. The highest chronic exposure was calculated for the NL toddler and DE child, representing 191% and 130% of the ADI, respectively. A second exposure calculation was therefore performed, excluding the CXLs for apples and pears, identified among the main contributors of the chronic exposure. According to the results of this second calculation, the highest chronic exposure declined to 91% of the ADI for NL toddler.

Recommendations

MRL recommendations were derived in compliance with the decision tree reported in Appendix E of the reasoned opinion (see Table 2). None of the MRL values listed in the table are recommended for inclusion in Annex II to the Regulation as they are not sufficiently supported by data. In particular, all tentative MRLs need to be confirmed by the following data:

1) Additional validation data supporting the analytical methods for enforcement in plant and animal commodities;
2) One additional residue trial compliant with the import tolerance indoor GAP on tomatoes.

It is underlined that some of the MRLs derived result from a CXL while the import tolerances were not fully supported by data. EFSA therefore identified the following data gap which is not expected to impact on the validity of the MRLs derived but which might have an impact on the import tolerances assessed:

- A representative storage stability study in livestock commodities.

It is furthermore highlighted that the ED properties of novaluron were not fully addressed. According to scenario 2a(iii) of the guidance for the identification of ED (ECHA/EFSA, 2018), further data should be generated:

- OECD TG 458 (AR STTA assay)
- OECD TG 456 (H295R steroidogenesis assay)
- OPPTS 890.1200 (Aromatase assay)

In case of negative results in the three studies, a Hershberger assay (OECD TG 441) should be performed. In case of positive results in one of the studies: OECD TG 443 or OECD TG 416 (2001) is requested.

Additional issues linked to missing data could not be finalised in the mammalian toxicology area:

- The impurities to which consumers may be exposed to are unknown.
- The analytical methods used in the repeated-dose toxicity studies were not reported, in particular for the 2-year oral toxicity study in rats that was used to derive the ADI.
- A residue definition for human biomonitoring (body fluids and tissues) is missing, i.e., an assessment of the metabolites of novaluron to be included in the residue definition for human biomonitoring (present in significant amounts in body fluids and/or in tissues).
- In the *in vitro* metabolism study submitted, the occurrence of unique human metabolites could not be fully ruled out.
- The neurotoxicity potential of novaluron was not addressed with regard to repeated-dose exposure.
- The immunotoxic and phototoxic potential of novaluron were not addressed.

These additional uncertainties should also be considered by risk managers during the decision-making process.

Table 2: Summary table

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
Residue definition for enforcement: novaluron(F)					
130010	Apples	2	3	–	Further consideration needed(b) data gap #1
130020	Pears	3	3	–	Further consideration needed(b) data gap #1
130030	Quinces	0.01*	3	3	Further consideration needed(c) data gap #1
130040	Medlar	0.01*	3	3	Further consideration needed(c) data gap #1
130050	Loquat	0.01*	3	3	Further consideration needed(c) data gap #1
140010	Apricots	2	7(a)	2	Further consideration needed(c) data gap #1
140020	Cherries	7	7	7	Further consideration needed(c) data gap #1
140030	Peaches	2	7(a)	2	Further consideration needed(c) data gap #1
140040	Plums	1.5	7(a)	1.5	Further consideration needed(c) data gap #1
152000	Strawberries	0.5	0.5	0.5	Further consideration needed(c) data gap #1
154010	Blueberries	7	7	7	Further consideration needed(d) data gap #1
154020	Cranberries	7	–	7	Further consideration needed(e) data gap #1
211000	Potatoes	0.2	0.01*	0.01*	Further consideration needed(c) data gap #1
231010	Tomatoes	1	0.7(a)	0.6	Further consideration needed(d) data gap #1 and # 2
231020	Peppers	0.6	0.7(a)	0.6	Further consideration needed(c) data gap #1
231030	Aubergines (egg plants)	0.5	0.7(a)	0.5	Further consideration needed(c) data gap #1
232010	Cucumbers	0.1	0.2(a)	0.1	Further consideration needed(c) data gap #1
232010	Gherkins	0.01*	0.2(a)	0.1	Further consideration needed(c) data gap #1
232030	Courgettes	0.1	0.2(a)	0.1	Further consideration needed(c) data gap #1
233010	Melons	0.2	0.2	0.2	Further consideration needed(c) data gap #1
233020	Pumpkins	0.2	0.2	0.2	Further consideration needed(c) data gap #1
233030	Watermelons	0.2	0.2	0.2	Further consideration needed(c) data gap #1
241010	Broccoli	0.6	0.7(a)	0.6	Further consideration needed(c) data gap #1
251070	Red mustard	25	25	25	Further consideration needed(c) data gap #1
252030	Beet leaves (chard)	15	15	15	Further consideration needed(c) data gap #1

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
260010	Beans (fresh, with pods)	0.7	0.7	0.7	Further consideration needed[c] data gap #1
260020	Beans (fresh, without pods)	0.7	0.7	0.7	Further consideration needed[c] data gap #1
300010	Beans (dry)	0.1	0.1	0.1	Further consideration needed[c] data gap #1
401070	Soya bean	0.01*	0.01*	0.01*	Further consideration needed[c] data gap #1
401090	Cotton seed	0.5	0.5	0.6	Further consideration needed[d] data gap #1
900020	Sugar cane	0.5	0.5	0.5	Further consideration needed[c] data gap #1
1011010	Swine meat	10	10	10	Further consideration needed[c] data gap #1
1011020	Swine fat (free of lean meat)	10	10	10	Further consideration needed[c] data gap #1
1011030	Swine liver	0.7	0.7	0.7	Further consideration needed[c] data gap #1
1011040	Swine kidney	0.7	0.7	0.7	Further consideration needed[c] data gap #1
1012010	Bovine meat	10	10	10	Further consideration needed[f] data gap #1
1012020	Bovine fat	10	10	10	Further consideration needed[f] data gap #1
1012030	Bovine liver	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1012040	Bovine kidney	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1013010	Sheep meat	10	10	10	Further consideration needed[f] data gap #1
1013020	Sheep fat	10	10	10	Further consideration needed[f] data gap #1
1013030	Sheep liver	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1013040	Sheep kidney	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1014010	Goat meat	10	10	10	Further consideration needed[f] data gap #1
1014020	Goat fat	10	10	10	Further consideration needed[f] data gap #1
1014030	Goat liver	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1014040	Goat kidney	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1015010	Horse meat	10	10	10	Further consideration needed[f] data gap #1
1015020	Horse fat	10	10	10	Further consideration needed[f] data gap #1
1015030	Horse liver	0.7	0.7	0.7	Further consideration needed[f] data gap #1
1015040	Horse kidney	0.7	0.7	0.7	Further consideration needed[f] data gap #1

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
1016010	Poultry meat	0.5	0.5	0.5	Further consideration needed[(c)] data gap #1
1016020	Poultry fat	0.5	0.5	0.5	Further consideration needed[(c)] data gap #1
1016030	Poultry liver	0.1	0.1	0.1	Further consideration needed[(c)] data gap #1
1020010	Cattle milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020020	Sheep milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020030	Goat milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020040	Horse milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1030000	Birds' eggs	0.1	0.1	0.1	Further consideration needed[(c)] data gap #1
–	Other commodities of plant and/or animal origin	See Reg. 441/2012	–	–	Further consideration needed[(g)]

MRL: maximum residue level; CXL: codex maximum residue limit.
*: Indicates that the MRL is set at the limit of quantification.
(F): The residue definition is fat soluble.
(a): These CXLs were not legally implemented in the EU, due to different extrapolation rules in line with the EFSA position for the CCPR (EFSA, 2011).
(b): GAP evaluated at EU level is not fully supported by data and a risk to consumers cannot be excluded; CXL is also not sufficiently supported by data and a risk to consumers cannot be excluded. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination E-IV in Appendix E).
(c): MRL is derived from the existing CXL, which is not sufficiently supported by data but for which no risk to consumers is identified; for apricots, peaches, plums, aubergines, sweet peppers, cucumbers, gherkins, courgettes and broccoli the CXL was recalculated considering the extrapolation rules applicable at EU level in line with the EFSA support for the EU position on the CCPR (EFSA, 2011); there are no relevant authorisations or import tolerances reported at EU level (combination A-V in Appendix E).
(d): 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; existing CXL (recalculated for tomatoes considering the extrapolation rules applicable at EU level in line with the EFSA support for the EU position on the CCPR (EFSA, 2011)) is covered by the tentative MRL (combination F-III in Appendix E).
(e): 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 F-I in Appendix E).
(f): MRL is derived from the existing CXL, which is not sufficiently supported by data but for which no risk to consumers is identified; GAP evaluated at EU level, which is also not fully supported by data, would lead to a lower tentative MRL (combination F-V in Appendix E).
(g): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available or existing CXLs were not legally implemented in the EU legislation since the EU delegation expressed a reservation (EFSA, 2011). Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination A-I in Appendix E).

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Abbreviations

AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
AUC	area under the blood concentration/time curve
BBCH	growth stages of mono- and dicotyledonous plants
bw	body weight
C_{max}	concentration achieved at peak blood level
CAC	Codex Alimentarius Commission
CCPR	Codex Committee on Pesticide Residues
cGAP	critical GAP
CXL	codex maximum residue limit
DAR	draft assessment report
DAT	days after treatment
DB	dietary burden
DM	dry matter
EATS	oestrogen, androgen, thyroid and steroidogenesis modalities
EC	emulsifiable concentrate
ECD	electron capture detector
ECHA	European Chemical Agency
ED	endocrine disruptor
EMS	evaluating Member State
eq	residue expressed as a.s. equivalent
EURLs	European Union Reference Laboratories for Pesticide Residues (former CRLs)
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
GC-ECD	gas chromatography with electron capture detector
Hg	haemoglobin
HR	highest residue
Ht	haematocrit
IEDI	international estimated daily intake
ILV	independent laboratory validation
InChiKey	International Chemical Identifier Key
ISO	International Organisation for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
LC_{50}	lethal concentration, median
LC–MS/MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observed adverse effect level
Mo	monitoring
MoA	mode of action
MRL	maximum residue level
MS	Member States
MW	molecular weight
NEDI	national estimated daily intake
NOAEL	no observed adverse effect level
NTMDI	national theoretical maximum daily intake

OECD	Organisation for Economic Co-operation and Development
PBI	plant-back interval
PF	processing factor
PHI	preharvest interval
P_{ow}	partition coefficient between *n*-octanol and water
PRIMo	(EFSA) Pesticide Residues Intake Model
PROFile	(EFSA) Pesticide Residues Overview File
QuEChERS	Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method)
RA	risk assessment
RBC	red blood cells
RAC	raw agricultural commodity
RD	residue definition
RMS	rapporteur Member State
SANCO	Directorate-General for Health and Consumers
SMILES	simplified molecular-input line-entry system
STMR	supervised trials median residue
$T_{1/2}$	half-life of elimination
T_{max}	time until peak blood levels achieved
TMDI	theoretical maximum daily intake
ToxCast	(US EPA) Toxicity Forecaster
TRR	total radioactive residue
UDS	unscheduled DNA synthesis
UF	uncertainty factor
WG	water-dispersible granule
WHO	World Health Organization

Appendix A – Summary of authorised uses considered for the review of MRLs

A.1. Import tolerances

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
				Type[b]	Conc. a.s.	Method kind	Range of growth stages & season[c]	Number min–max	Interval Between application (min)	a.s./ hL min–max	Water L/ha min–max	Rate and unit		
Apples	US	F	Various biting and sucking insects	WG	75 g/kg	Foliar treatment	–	4	10	–	–	370 g a.s./ha	14	
Pears	US	F	Various biting and sucking insects	EC	100 g/L	Foliar treatment	–	4	10	–	–	370 g a.s./ha	14	
Blueberries	US	F	Various biting and sucking insects	EC	100 g/L	Foliar treatment	–	3	7	–	–	218 g a.s./ha	8	
Cranberries	US	F	Various biting and sucking insects	EC	100 g/L	Foliar treatment	–	3	7	–	–	218 g a.s./ha	8	
Tomatoes	US	I	Various biting and sucking insects	EC	100 g/L	Foliar treatment	–	3	7	–	–	90 g a.s./ha	1	
Cotton seeds	US	F	Various biting and sucking insects	EC	100 g/L	Foliar treatment	–	4	7	–	–	100 g a.s./ha	30	

MS: Member State; a.s.: active substance; EC: emulsifiable concentrate; WG: water-dispersible granule.
(a): Outdoor or field use (F), greenhouse application (G) or indoor application (I).
(b): CropLife International Technical Monograph no 2, 7th Edition. Revised March 2017. Catalogue of pesticide formulation types and international coding system. 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.
(c): PHI: minimum preharvest interval.

Appendix B – List of end points

B.1. Mammalian Toxicology

Impact on Human and Animal Health

Rate and extent of oral absorption/systemic bioavailability	Ca. 6-9% at the low dose level of 2 mg/kg bw and 0.7% at the high dose level of 1,000 mg/kg bw (chlorophenyl moiety) based on urinary and biliary excretion within 48 h Up to 21% for the difluorophenyl moiety (based on urinary excretion, carcass and tissues within 168 h after single administration – difluorophenyl-^{14}C); the difluorophenyl moiety presented higher urinary excretion that may corelate to higher oral absorption (however, this value could be an overestimate since it is not clear if any cleavage of the molecule will occur in the gastrointestinal tract prior to absorption and will alter the absorption).
Toxicokinetics	Blood C_{max} , T_{max} , AUC, Plasma $T_{1/2}$

Dose level (mg/kg bw (per day))	Blood C_{max} (mg equiv/g)	Blood T_{max} (h)	Blood AUC_{168} (mg equiv.h/g)	Plasma $T_{1/2}$ (h)[a]	C_{max} ratio (blood: plasma)
2 (CP)	0.03	8	1.08-1.98	15	0.92-1.18
2 (DF)	0.04-0.05	5-8	0.85-0.88	12	1.02-1.03
14x2 (CP)	0.08-0.10	2-8	9.52-11.3	137-242	1.67-2.90
1000 (CP)	1.58-1.96	2-5	8.31-26.8	19	0.65-0.85

CP: [Chlorophenyl-^{14}C(U)]novaluron

DF: [Difluorophenyl-^{14}C(U)]novaluron

[a]values are an estimate as the interval including the data points chosen for regression was at least 2x t½

Distribution	Widely distributed, greatest levels in fat, liver, kidneys, adrenals, pancreas and mesenteric lymph nodes. Other tissues containing relatively high concentrations of radioactivity included the intraorbital and exorbital lachrymal glands, Harderian gland, salivary glands, prostate and nasal mucosa (and the tooth root after administration of the [difluorophenyl-$_{14}$C (U)]-labelled compound)

Potential for bioaccumulation	Accumulation of radioactivity over repeated exposure as shown by an increase in AUC_{168} values for plasma by a factor of 5 over a single low dose. Blood and plasm half-lives were markedly prolonged in the repeated dose group.
Rate and extent of excretion	Rapid excretion mainly via faeces (> 80% within 48 h), slower excretion via urine (5% within 168 h); biliary excretion appears to be of minor importance for elimination (study of low reliability)
Metabolism in animals	The small absorbed portion underwent extensive metabolism, mainly by cleavage of the urea bridge between the chlorophenyl and difluorophenyl moieties. The majority of faecal radioactivity consisted of unchanged parent (71.9–88.0% of administered dose); the main metabolite identified in urine is metabolite 257-158 I (2,6-difluorobenzoic acid), major metabolite up to 12% of administered dose; other metabolites accounted for ≤ 1% of the administered dose and around 1% of metabolite 275-309 I (3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline), the chlorophenyl aniline derivative of novaluron.
In vitro metabolism	No human-specific metabolite identified, however, cannot be completely excluded as the test item was converted to a higher % than the negative control. Higher conversion found in rabbits (one peak above 5% of total radioactivity) > rats > dogs > mice > humans (no peak identified for either mice or humans. The two peaks obtained were not identified.
Toxicologically relevant compounds (animals and plants)	Parent compound (novaluron)
Toxicologically relevant compounds (environment)	No data, data not relevant to import tolerances

Acute toxicity (Regulation (EU) No 283/2013, Annex Part A, point 5.2)

Rat LD_{50} oral	> 5,000 mg/kg bw (in rat and mouse)	
Rat LD_{50} dermal	No data, data not relevant to import tolerances	
Rat LC_{50} inhalation	> 5.15 mg/L air per 4 h (nose only)	
Skin irritation	No data, data not relevant to import tolerances	
Eye irritation	No data, data not relevant to import tolerances	
Skin sensitisation	No data, data not relevant to import tolerances	
Phototoxicity	No data, data not relevant to import tolerances	

Short-term toxicity (Regulation (EU) No 283/2013, Annex Part A, point 5.3)

Target organ / critical effect	Rat: ↑ bw gain, ↑ triglyceride, signs indicative of anaemia (↓ RBC, Hg, Ht, extramedullary haematopoiesis, hemosiderin pigments in spleen and ↑ spleen weight) Mouse: inclusion bodies in reticulocyte smear; (↑ bw, anaemia at higher dose levels) Dog: ↑ reticulocytes and sulfhaemoglobin (signs indicative of regenerative haemolytic anaemia)	
Relevant oral NOAEL	90-day, rat: 0.7 mg/kg bw per day 90-day, mouse: LOAEL 4.2 mg/kg bw per day 90-day, dog: LOAEL 10 mg/kg bw per day	
Relevant dermal NOAEL	14-day, rat: $LOAEL_{systemic}$ 10 mg/kg bw per day (↑ bw gain) 14-day, rat $NOAEL_{local}$ 10 mg/kg bw per day (scab formation)	
Relevant inhalation NOAEL	No data – not required	

Genotoxicity (Regulation (EU) No 283/2013, Annex Part A, point 5.4)

In vitro studies	Negative Ames tests Equivocal bacterial DNA repair assay (-S9); negative (+S9) (test with drawbacks) *(No OECD TG available, poor performance of one of the positive controls)* Negative mammalian cell DNA repair assay (UDS)(*OECD TG 482 deleted; results not relevant)* Negative chromosome aberration test in human lymphocytes Negative gene mutation (mouse lymphoma) assay Negative micronucleus assay	
In vivo studies	Micronucleus test (negative but with insufficient evidence of bone marrow exposure)	
Photomutagenicity	No data, justification for waiving not provided	
Potential for genotoxicity	Novaluron is unlikely to be genotoxic based on *in vitro* tests	

Long-term toxicity and carcinogenicity (Regulation (EU) No 283/2013, Annex Part A, point 5.5)

Long-term effects (target organ/critical effect)	Rat: Haematological changes indicative of haemolytic anaemia (↓ RBC and Hg, ↑ reticulocytes, methaemoglobin formation, Howell jolly bodies, hemosiderosis in spleen, ↑ spleen weight), liver (periacinar hepatocytic hypertrophy) Mouse: ↑ reticulocytes and Heinz bodies (↑ bw gain; haematological changes indicative of regenerative haemolytic anaemia; ↑ spleen weight; cortical tubular pigment in kidneys at higher dose levels)	
Relevant long-term NOAEL	2-year, rat: 1.1 mg/kg bw per day 18-month, mouse: LOAEL: 3.6 mg/kg bw per day	
Carcinogenicity (target organ, tumour type)	Rat: no statistically significant increase in tumours was observed Mouse: no statistically or biologically significant increase in tumours was observed. Novaluron is unlikely to pose a hazard to humans	
Relevant NOAEL for carcinogenicity	2-year, rat: 884.2 mg/kg bw per day (highest dose tested) 18-month, mouse: 800 mg/kg bw per day (highest dose tested)	

Reproductive toxicity (Regulation (EU) No 283/2013, Annex Part A, point 5.6)

Reproduction toxicity

Reproduction target / critical effect	Parental toxicity: ↑ body weight and spleen weight Reproductive toxicity: ↓ epididymal sperm, changes in oestrus cycle Offspring's toxicity: ↑ body weight, ↑ spleen and liver weight; delayed preputial separation	
Relevant parental NOAEL	LOAEL 74 mg/kg bw per day	
Relevant reproductive NOAEL	LOAEL 74 mg/kg bw per day	
Relevant offspring NOAEL	LOAEL 74 mg/kg bw per day	

Developmental toxicity

Developmental target / critical effect	Rat: Maternal toxicity: ↑ body weight Developmental toxicity: ↓ corpora lutea, ↓ implantations, ↑ post – implantation loss Rabbit:	

	Maternal toxicity: ↓ weight gain Developmental toxicity: ↑ incompletely ossified 5th sternebrae	
Relevant maternal NOAEL	Rat: LOAEL 250 mg/kg bw per day Rabbit: 300 mg/kg bw per day	
Relevant developmental NOAEL	Rat: 500 mg/kg bw per day Rabbit: 100 mg/kg bw per day	

Neurotoxicity (Regulation (EU) No 283/2013, Annex Part A, point 5.7)

Acute neurotoxicity	Rat: $NOAEL_{(neurotoxicity)}$ 2000 mg/kg bw (highest dose tested); no sign of a specific neurotoxic potential $LOAEL_{(general\ toxicity)}$ 200 mg/kg bw (fast respiration, piloerection and irritable behaviour)	
Repeated neurotoxicity	No data – data needed	
Additional studies (e.g., delayed neurotoxicity, developmental neurotoxicity)	No data	

Other toxicological studies (Regulation (EU) No 283/2013, Annex Part A, point 5.8)

Supplementary studies on the active substance	Published literature was retrieved in July 2020. In a publication, no side effects were observed following a pour-on treatment on the back of cattle at dose levels of 1 mg/20 kg bw and 1 mg/10 kg bw (however insufficient for use against cattle ticks). Another publication hypothesised that the cause of novaluron treatment-related anaemia is a metabolite (nitrosoaniline derivative) that could enter the RBC, react with oxyhaemoglobin and start a chain reaction resulting in a change of erythrocyte cell surface properties. This could lead to premature activation of the autoimmune-mediated mechanism, by which RBC are phagocytised in the spleen. It is plausible that the observed anaemia may be caused by oxidative injury to RBC, however, the exact MoA is not known. Immunotoxicity not addressed.

Endocrine disrupting properties	T-modality: The criteria are not met for the T-modality in a sufficiently investigated dataset. EAS-modalities: The data set is not complete for the AS modalities, some EAS mediated endpoints were affected (spermiogenesis and oestrus cycle), but these were not considered sufficient to indicate that an AS-mediated pattern of adversity exists. No additional studies are necessary to investigate the E modality since the ToxCast E-model is negative. Further data should be generated according to scenario 2a(iii): - OECD TG 458 (stably transfected AR transcriptional activation assay) - OECD TG 456 (H295R steroidogenesis assay) - OPPTS 890.1200 (aromatase assay), If negative results in the three studies, OECD TG 441 (Hershberger assay) should be performed. If positive results in one of the studies, OECD TG 443 or 416 (2001) is requested Non-EATS-mediated modalities: Uncertainties exist on potential for novaluron to affect non-EATS mediated endocrine pathways, in particular a concern exists for an endocrine disrupting action on metabolism (e.g. metabolic syndrome), this is mainly based on the recurrent observations in the data set, of increase in bw gain in the absence of an increase in food consumption, increase in serum cholesterol, triglycerides and glucose levels. In line with the EFSA/ECHA guidance and lacking clear testing and MoA for non-EATS-mediated pathways, the ED assessment for non-EATS pathway will remain inconclusive. All available data in ToxCast investigating non-EATS mediated molecular initiating events should be reported and weighted as part of the ED assessment.

Studies performed on metabolites or impurities	Metabolite 275-158-I (2,6-difluorobenzoic acid): As major metabolite observed in the rat metabolism studies, toxicological reference values of the parent apply to this metabolite. Metabolite 275-309-I (3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline): As major metabolite observed in the rat metabolism studies (considering the retrieved radioactivity in urine corrected by low oral absorption), toxicological reference values of the parent apply to this metabolite. Metabolite 275-352-I (1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]urea): No data available Impurities: *Impurity MCW RI 458*: Rat acute oral LD50 > 5,000 mg/kg bw Ames test negative *Impurity MCW I:* Ames test negative

Medical data (Regulation (EU) N° 283/2013, Annex Part A, point 5.9)

No data – data needed A report of pesticide poisoning incident in farm workers exposed to off-target drift of a pesticide mixture could not determine if one active ingredient was responsible for the symptoms or several acting in concert.

Summary (Regulation (EU) N°1107/2009, Annex II, point 3.1 and 3.6)

	Value (mg/kg bw (per day))	Study	Uncertainty factor
Acceptable Daily Intake (ADI)	0.01	rat, 2-year study	100
Acute Reference Dose (ARfD)	Not established, not necessary	-	-
Acceptable Operator Exposure Level (AOEL)	Not established, not relevant to import tolerances	-	-
Acute Acceptable Operator Exposure Level (AAOEL)	Not established, not relevant to import tolerances	-	-

Dermal absorption (Regulation (EU) No 284/2013, Annex Part A, point 7.3)

Representative formulation (*indicate name, type e.g.* EC *and concentration of active substance*)	No data, not relevant to import tolerances

Exposure scenarios (Regulation (EU) No 284/2013, Annex Part A, point 7.2)

Operators	No data, not relevant to import tolerances
Workers	No data, not relevant to import tolerances
Bystanders and residents	No data, not relevant to import tolerances

Classification with regard to toxicological data (Regulation (EU) No 283/2013, Annex Part A, Section 10)

Substance:	Novaluron
Harmonised classification according to Regulation (EC) No 1272/2008 and its Adaptations to Technical Process [Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended][11]:	Currently, no harmonised classification
Peer review proposal[12] for harmonised classification according to Regulation (EC) No 1272/2008:	None proposed

[11] 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, 1–1355.

[12] It should be noted that harmonised classification and labelling is formally proposed and decided in accordance with Regulation (EC) No 1272/2008.

B.2. Residues in plants

B.2.1. Nature of residues and methods of analysis in plants

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

Primary crops (available studies)	**Crop groups**	**Crops**	**Applications**	**Sampling (DAT)**	**Comment/Source**
	Fruit crops	apples	Foliar, 2–3 × 50–80 g a.s./ha	30, 60, 90	Radiolabelled novaluron: chlorophenyl-^{14}C and difluorophenyl-^{14}C (The United Kingdom, 2005; Germany, 2020)
	Root crops	potatoes	Foliar, 2 × 91–100 g a.s./ha	7, 19, 29	
	Leafy crops	cabbage	Foliar, 2 × 30–45 g a.s./ha	7, 14, 28, 42	
	Pulses/oilseeds	cotton seed	Foliar, 2 × 50 g a.s./ha	30, 44, 60, 90, 104	
Rotational crops (available studies)	**Crop groups**	**Crop(s)**	**Application(s)**	**PBI (DAT)**	**Comment/Source**
	Root/tuber crops	turnip	Bare soil, 1 × 100 g a.s./ha	30, 65, 99–127	Radiolabelled novaluron: chlorophenyl-^{14}C (The United Kingdom, 2005; Germany, 2020). Available but not required as novaluron is no longer authorised in Europe.
	Leafy crops	spinach	Bare soil, 1 × 100 g a.s./ha	30, 65, 98–132	
	Cereal (small grain)	wheat	Bare soil, 1 × 100 g a.s./ha	30, 85, 163–195	
Processed commodities (hydrolysis study)	**Conditions**		**Stable?**		**Comment/Source**
	Pasteurisation (20 min, 90°C, pH 4)		Not triggered		Hydrolysis studies not required since novaluron has a water solubility of 0.003 mg/L (below < 0.01 mg/L). It is noted that in a previous EFSA reasoned opinion on novaluron a hydrolysis study was reported (EFSA, 2010). Nevertheless, for the reason above, results from this study were not considered further in the assessment.
	Baking, brewing and boiling (60 min, 100°C, pH 5)		Not triggered		
	Sterilisation (20 min, 120°C, pH 6)		Not triggered		

Can a general residue definition be proposed for primary crops?	yes	
Rotational crop and primary crop metabolism similar?	Not applicable	Only import tolerances assessed, as novaluron is no longer authorised in Europe. All crop samples showed total residues of less than 0.01 mg/kg equivalent, thus further characterisation was not performed.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable	Data are not required considering the low solubility of novaluron in water.
Plant residue definition for monitoring (RD-Mo)	novaluron	
Plant residue definition for risk assessment (RD-RA)	novaluron	
Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs)	Matrices with high water content: LC-MS/MS, LOQ 0.01 mg/kg Confirmatory method available. ILV missing (data gap). (Germany, 2020) Matrices with high acid content: GC-ECD, LOQ 0.01 mg/kg Confirmatory method ILV missing (data gap). (Germany, 2020) For commodities with high fat content and for dry crops analytical methods are missing (data gap). Additional validation data for novaluron is provided by the EURLs indicating the applicability of the QuEChERS method with LC-MS/MS detection for high water content, high acid and dry commodities with at least a LOQ of 0.01 mg/kg (EURLs, 2020). For high oil content matrices, the EURLs report indicates the applicability of the QuOil method with LC-MS/MS detection and a LOQ of 0.01 mg/kg.	

a.s.: active substance; DAT: days after treatment; PBI: plant-back interval; GC-ECD: gas chromatography with electron capture detector; LC–MS/MS: liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

B.2.1.2. Stability of residues in plants

Plant products (available studies)	Category	Commodity	T (°C)	Stability period		Compounds covered	Comment/Source
				Value	Unit		
	High water content	Apples, cabbage, broccoli	Frozen	6	Months	Novaluron	United Kingdom (2005), Germany (2020)
		Tomatoes	–18	12	Months	Novaluron	United Kingdom (2005), Germany (2020)
	High oil content	Cotton seed;	–20	5	Months	Novaluron	Germany (2020)
	High starch content	Potato	–18	6	Months	Novaluron	United Kingdom (2005), Germany (2020)
	High acid content	Blueberries	–38 to –0.2	5	Months	Novaluron	Stable up to 141 days (EFSA, 2010)
	Dry matrices	Cotton gin trash	–20	5	Months	Novaluron	Germany (2020)
	Processed products	Orange peel, marmalade, dry pomace and wet pomace	–18	6	Months	Novaluron	Germany (2020)

B.2.2. Magnitude of residues in plants

B.2.2.1. Summary of residues data from the supervised residue trials – Primary crops

Commodity	Region/ Indoor[a]	Residue levels observed in the supervised residue trials (mg/kg)	Comments/Source	Calculated MRL (mg/kg)	HR[b] (mg/kg)	STMR[c] (mg/kg)
Apples Pears	Import (US)	Apples: 0.27; 0.35[g]; 0.44[g]; 0.44[g]; 0.49; 2 × 0.5; 0.54[g]; 0.6; 0.67; 0.68; 0.71[g]; 0.78[g]; 0.81[g]; 0.86[g]; 0.93[g]; 0.96[g]; 1.1[g] Pears: 0.46; 0.48[g]; 0.79[g]; 0.92[g]; 1.0[g]; 1.3[g]; 1.6[g]; 1.8[g]	Combined data set of trial on apples and pears compliant with GAP or performed with 6 instead of 3 applications (Germany, 2020). MRL_{OECD} = 2.26	**3** (tentative)[d]	1.80	0.70
Blueberries Cranberries	Import (US)	0.82; 0.84; 0.86; 1.72; 1.95; 3.25; 3.36	Trials on blueberries compliant with GAP (Germany, 2020). Extrapolation to cranberries is applicable (EFSA, 2010). MRL_{OECD} = 6.29	**7** (tentative)[e]	3.36	1.72
Tomatoes	Import (US)	< 0.05; 0.15; 0.17; 0.22; 0.23; 0.23; 0.37	Trials on tomatoes compliant with GAP (Germany, 2020). MRL_{OECD} = 0.59	**0.6** (tentative)[d,i]	0.37	0.22

Commodity	Region/ Indoor[a]	Residue levels observed in the supervised residue trials (mg/kg)	Comments/Source	Calculated MRL (mg/kg)	HR[b] (mg/kg)	STMR[c] (mg/kg)
Cotton seeds	Import (US)	3 × < 0.05[h]; 0.05; 2 × 0.06[h]; 0.07[h]; 0.1; 0.23; 0.25[h]; 0.4[h]	Trials on cotton seed compliant with GAP or performed with 5 instead of 4 applications (Germany, 2020). MRL_{OECD} = 0.59	**0.6** (tentative)[f]	0.40	0.06

GAP: Good Agricultural Practice; OECD: Organisation for Economic Co-operation and Development; MRL: maximum residue level.
Mo: residue levels expressed according to the monitoring residue definition; RA: residue levels expressed according to risk assessment residue definition.
(a): NEU: Outdoor trials conducted in northern Europe, SEU: Outdoor trials conducted in southern Europe, Indoor: indoor EU trials or Country code: if non-EU trials.
(b): Highest residue.
(c): Supervised trials median residue.
(d): MRL is tentative because ILV for the analytical method is missing.
(e): MRL is tentative because confirmatory method and ILV are missing.
(f): MRL is tentative because analytical method is missing.
(g): Results from trials performed with 6 applications (3 early season + 3 late season) acceptable since early season applications do not contribute to the final residue level.
(h): Results from trials performed with 5 applications instead of 4 are acceptable since early season applications do not contribute to the final residue level.
(i): MRL is tentative because one additional trial is needed.

B.2.2.2. Residues in rotational crops

a) Overall summary

Residues in rotational and succeeding crops expected based on confined rotational crop study?	Not triggered	Since novaluron is not approved in the EU and the only uses under assessment are import tolerances, consideration on rotational crops is not required.
Residues in rotational and succeeding crops expected based on field rotational crop study?	Not triggered	Since novaluron is not approved in the EU and the only uses under assessment are import tolerances, consideration on rotational crops is not required.

B.2.2.3. Processing factors

Processed commodity	Number of valid studies[a]	Processing Factor (PF)		Comment/Source
		Individual values	Median PF	
Apples, juice	7	< 0.03; < 0.03; < 0.06; < 0.1; < 0.1; < 0.1; < 0.1;	< 0.1	Germany (2020)
Apples, wet pomace	7	2.6, 2.8, 3.1, 4.4, 5.2, 6.2, 7.7	4.4	Germany (2020)
Apples, dry pomace	6	12, 15, 17, 17, 20, 24	17	Germany (2020)
Tomato, peeled and canned	3	< 0.25; < 0.33; < 0.33	< 0.33	Germany (2020)

Processed commodity	Number of valid studies[a]	Processing Factor (PF)		Comment/Source
		Individual values	Median PF	
Tomato, paste	1	1.1	1.1	Tentative[b] (Germany, 2020)
Tomato, juice	3	0.25; < 0.66; 0.66	< 0.66	Germany (2020)
Tomato, puree	4	< 0.73; 1.5; 4.25; 4.67	2.5	Germany (2020)
Plums, dried	2	n.r.	3.1	Tentative[b] (Germany, 2020)
Cotton, meal	1	< 0.6	< 0.6	Tentative[b] (Germany, 2020)
Cotton, hulls	1	< 0.6	< 0.6	Tentative[b] (Germany, 2020)
Cotton, refined oil	1	< 0.6	< 0.6	Tentative[b] (Germany, 2020)

PF: Processing factor (=Residue level in processed commodity expressed according to RD-Mo/ Residue level in raw commodity expressed according to RD-Mo).
Studies with residues in the RAC at or close to the LOQ were disregarded (unless concentration may occur).
(a): n.r.: not reported.
(b): A tentative PF is derived based on a limited data set.

B.3. Residues in livestock

Relevant groups (subgroups)	Dietary burden expressed in				Most critical subgroup[a]	Most critical commodity[b]	Trigger exceeded (Y/N)	Comments
	mg/kg bw per day		mg/kg DM					
	Median	Maximum	Median	Maximum				
Cattle (all diets)	0.037	0.037	1.53	1.53	Beef cattle	Apple, wet pomace	Y	–
Cattle (dairy only)	0.030	0.030	0.77	0.77	Dairy cattle	Apple, wet pomace	Y	–
Sheep (all diets)	0.032	0.032	0.76	0.76	Lamb	Apple, wet pomace	Y	–
Sheep (ewe only)	0.025	0.025	0.76	0.76	Ram/Ewe	Apple, wet pomace	Y	–
Swine (all diets)	0.000	0.000	0.00	0.00	Swine (breeding)	Cotton, meal	N	–
Poultry (all diets)	0.000	0.000	0.00	0.00	Turkey	Cotton, meal	N	–
Poultry (layer only)	0.000	0.000	0.00	0.00	Poultry layer	Cotton, meal	N	–

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

B.3.1. Nature of residues and methods of analysis in livestock

B.3.1.1. Metabolism studies, methods of analysis and residue definitions in livestock

Livestock (available studies)	**Animal**	**Dose (mg/kg bw per day)**	**Duration (days)**	**Comment/Source**
	Laying hen	0.68	14	Radiolabelled novaluron: difluoropheny-^{14}C (Germany, 2020)
	Lactating ruminants	0.31–0.34	5	Study on goat. Radiolabelled novaluron: difluoropheny-^{14}C and chloropheny-^{14}C (Germany, 2020). Dose rate originally reported as 11-12 mg/kg feed per animal recalculated assuming body weight of 70 kg and feed intake of 2 kg/day.
	Pig	–	–	Not available and not required (metabolism in ruminants and rat similar and dietary burden for swine not triggered)

Time needed to reach a plateau concentration in milk and eggs (days)	Milk: 28–39 days Eggs: 19 days	From feeding studies (Germany, 2020). Residues in milk plateaued between day-28 and day-39 depending on the dose group and when adjusting for milk yield of animals in feeding study (Germany, 2020).
Metabolism in rat and ruminant similar	Yes	
Can a general residue definition be proposed for animals?	Yes	
Animal residue definition for monitoring (RD-Mo)	Novaluron	
Animal residue definition for risk assessment (RD-RA)	Novaluron	
Fat soluble residues	Yes	$\log_{10}P_{ow}$ of 4.3 at 20 °C (United Kingdom, 2005)
Methods of analysis for monitoring of residues (analytical technique, matrix groups, LOQs)	Confirmatory method available for tissues and milk but missing for eggs. ILV missing for all livestock commodities. (Germany, 2020) EURLs indicated the applicability of the QuEChERS method with C18 clean-up and LC-MS/MS detection with an LOQ of 0.01 mg/kg in muscle, liver, milk and egg (EURLs, 2020).	

bw: body weight; Pow: partition coefficient between n-octanol and water; GC-ECD: gas chromatography with electron capture detector; LC -MS/MS: liquid chromatography with tandem mass spectrometry; LOQ: limit of quantification; ILV: independent laboratory validation.

B.3.1.2. Stability of residues in livestock

Storage stability studies are missing and are required.

B.3.2. Magnitude of residues in livestock

B.3.2.1. Summary of the residue data from livestock feeding studies

Animal commodity	Residues at the closest feeding level (mg/kg)		Estimated value at 1N		MRL proposal (mg/kg)
	Mean	Highest	$STMR_{Mo}$[a] (mg/kg)	HR_{Mo}[b] (mg/kg)	
Cattle (all) – Closest feeding level (0.088 mg/kg bw; 2.4N rate)[c]					
Muscle	0.08	0.09	0.03	0.04	**0.04** (tentative)[f]
Fat	1.02	1.24	0.43	0.52	**0.6** (tentative)[f]
Liver	0.13	0.14	0.05	0.06	**0.06** (tentative)[f]
Kidney	0.13	0.14	0.05	0.06	**0.06** (tentative)[f]
Cattle (dairy only) – Closest feeding level (0.088 mg/kg bw; × 3N rate)[c]					
Milk[d]	0.13	0.15	0.04	0.04	**0.05** (tentative)[f]
Sheep (all)[e] – Closest feeding level (0.088 mg/kg bw; 2.7N rate)[c]					
Muscle	0.08	0.09	0.03	0.03	**0.04** (tentative)[f]
Fat	1.02	1.24	0.38	0.46	**0.5** (tentative)[f]
Liver	0.13	0.14	0.05	0.05	**0.06** (tentative)[f]
Kidney	0.13	0.14	0.05	0.05	**0.06** (tentative)[f]
Sheep (ewe only)[e] – Closest feeding level (0.088 mg/kg bw; × 3.5N rate)[c]					
Milk[d]	0.13	0.15	0.04	0.04	**0.04** (tentative)[f]
Swine (all) – not triggered					
Poultry (all) – not triggered					
Poultry (layer only) – not triggered					

bw: body weight; n.a.: not applicable; n.r.: not reported.
*: Indicates that the MRL is proposed at the limit of quantification.
(a): Median residues expressed according to the residue definition for monitoring, recalculated at the 1N rate for the median dietary burden.
(b): Highest residues expressed according to the residue definition for monitoring, recalculated at the 1N rate for the maximum dietary burden.
(c): Closest feeding level and N dose rate related to the maximum dietary burden.
(d): For milk, mean was derived from samplings performed from day 1 to day 42 (daily mean of 21 cows).
(e): Since extrapolation from cattle to other ruminants and swine is acceptable, results of the livestock feeding study on ruminants were relied upon to derive the MRL and risk assessment values in sheep.
(f): MRL is tentative because fully validated methods (ILV is missing) and storage stability in livestock commodities are not available.

B.4. Consumer risk assessment

B.4.1. Consumer risk assessment without consideration of the existing CXLs

Not relevant since no ARfD has been considered necessary.

ADI	0.01 mg/kg bw per day (EFSA, 2021)
TMDI according to EFSA PRIMo	Not assessed in this review.
NTMDI, according to (to be specified)	Not assessed in this review.
Highest IEDI, according to EFSA PRIMo (rev.3.1)	**Scenario EU1 (without risk mitigation measures):** 135% ADI (NL, toddler) 103% ADI (DE, child) Main contributors: Results for NL, toddler: Apples: 75% of ADI Pears: 30% of ADI Milk (cattle): 26% of ADI Results for DE, child: Apples: 87% of ADI Milk (cattle): 9% of ADI Pears: 5% of ADI **Scenario EU2 (with risk mitigation measures):** 61% ADI (NL, toddler) Main contributor: Pears: 30% of ADI
NEDI (% ADI)	Not assessed in this review.
Assumptions made for the calculations	**Scenario EU1 (without risk mitigation measures):** The calculation is based on the median residue levels derived for raw agricultural commodities. The contributions of commodities where no GAP was reported in the framework of the MRL review were not included in the calculation. **Scenario EU2 (with risk mitigation measures):** For apples no fall-back option was identified, thus this commodity was removed from the calculations assuming that the GAP on this crop will be withdrawn. All other input values remain unchanged.

ADI: acceptable daily intake; bw: body weight; NEDI: national estimated daily intake; PRIMo: (EFSA) Pesticide Residues Intake Model; WHO: World Health Organization; TMDI: theoretical maximum daily intake; NTMDI: national theoretical maximum daily intake.

Consumer exposure assessment through drinking water resulting from groundwater metabolite(s) according to SANCO/221/2000 rev.10 Final (25/02/2003)

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

B.4.2. Consumer risk assessment with consideration of the existing CXLs

Not relevant since no ARfD has been considered necessary.

ADI	0.01 mg/kg bw per day (EFSA, 2021)
TMDI according to EFSA PRIMo	Not assessed in this review.
NTMDI, according to (to be specified)	Not assessed in this review.
Highest IEDI, according to EFSA PRIMo (rev.3.1)	**Scenario CX1:** 191% ADI (NL, toddler) 130% ADI (DE, child) Main contributors: Results for NL, toddler: Milk (cattle): 78% of ADI Apples: 70% of ADI Pears: 30% of ADI Results for DE, child: Apples: 81% of ADI Milk (cattle): 26% of ADI Cherries sweet: 8% of ADI **Scenario CX2:** 91% ADI (NL, toddler) Main contributor: Milk (cattle): 78% of ADI
NEDI (% ADI)	Not assessed in this review.
Assumptions made for the calculations	**Scenario CX1:** For those commodities having a CXL higher than the EU MRL proposal, median residue levels applied in the second EU scenario were replaced by the median residue levels derived by JMPR. The calculation is based on the median residue levels derived for raw agricultural commodities. The contributions of commodities where no GAP was reported in the framework of the MRL review were not included in the calculation. **Scenario CX2:** For apples and pears no fall-back option was identified, thus these commodities were removed from the calculations. All other input values remain unchanged.

ADI: acceptable daily intake; bw: body weight; NEDI: national estimated daily intake; PRIMo: (EFSA) Pesticide Residues Intake Model; TMDI: theoretical maximum daily intake; NTMDI: national theoretical maximum daily intake.

B.5. Proposed MRLs

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
Residue definition for enforcement: novaluron(F)					
130010	Apples	2	3	–	Further consideration needed(b) data gap #1
130020	Pears	3	3	–	Further consideration needed(b) data gap #1
130030	Quinces	0.01*	3	3	Further consideration needed(c) data gap #1
130040	Medlar	0.01*	3	3	Further consideration needed(c) data gap #1
130050	Loquat	0.01*	3	3	Further consideration needed(c) data gap #1
140010	Apricots	2	7(a)	2	Further consideration needed(c) data gap #1
140020	Cherries	7	7	7	Further consideration needed(c) data gap #1
140030	Peaches	2	7(a)	2	Further consideration needed(c) data gap #1
140040	Plums	1.5	7(a)	1.5	Further consideration needed(c) data gap #1
152000	Strawberries	0.5	0.5	0.5	Further consideration needed(c) data gap #1
154010	Blueberries	7	7	7	Further consideration needed(d) data gap #1
154020	Cranberries	7	–	7	Further consideration needed(e) data gap #1
211000	Potatoes	0.2	0.01*	0.01*	Further consideration needed(c) data gap #1
231010	Tomatoes	1	0.7(a)	0.6	Further consideration needed(d) data gap #1 and #2
231020	Peppers	0.6	0.7(a)	0.6	Further consideration needed(c) data gap #1
231030	Aubergines (egg plants)	0.5	0.7(a)	0.5	Further consideration needed(c) data gap #1
232010	Cucumbers	0.1	0.2(a)	0.1	Further consideration needed(c) data gap #1
232010	Gherkins	0.01*	0.2(a)	0.1	Further consideration needed(c) data gap #1
232030	Courgettes	0.1	0.2(a)	0.1	Further consideration needed(c) data gap #1
233010	Melons	0.2	0.2	0.2	Further consideration needed(c) data gap #1
233020	Pumpkins	0.2	0.2	0.2	Further consideration needed(c) data gap #1
233030	Watermelons	0.2	0.2	0.2	Further consideration needed(c) data gap #1
241010	Broccoli	0.6	0.7(a)	0.6	Further consideration needed(c) data gap #1
251070	Red mustard	25	25	25	Further consideration needed(c) data gap #1

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
252030	Beet leaves (chard)	15	15	15	Further consideration needed[(c)] data gap #1
260010	Beans (fresh, with pods)	0.7	0.7	0.7	Further consideration needed[(c)] data gap #1
260020	Beans (fresh, without pods)	0.7	0.7	0.7	Further consideration needed[(c)] data gap #1
300010	Beans (dry)	0.1	0.1	0.1	Further consideration needed[(c)] data gap #1
401070	Soya bean	0.01*	0.01*	0.01*	Further consideration needed[(c)] data gap #1
401090	Cotton seed	0.5	0.5	0.6	Further consideration needed[(d)] data gap #1
900020	Sugar cane	0.5	0.5	0.5	Further consideration needed[(c)] data gap #1
1011010	Swine meat	10	10	10	Further consideration needed[(c)] data gap #1
1011020	Swine fat (free of lean meat)	10	10	10	Further consideration needed[(c)] data gap #1
1011030	Swine liver	0.7	0.7	0.7	Further consideration needed[(c)] data gap #1
1011040	Swine kidney	0.7	0.7	0.7	Further consideration needed[(c)] data gap #1
1012010	Bovine meat	10	10	10	Further consideration needed[(f)] data gap #1
1012020	Bovine fat	10	10	10	Further consideration needed[(f)] data gap #1
1012030	Bovine liver	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1012040	Bovine kidney	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1013010	Sheep meat	10	10	10	Further consideration needed[(f)] data gap #1
1013020	Sheep fat	10	10	10	Further consideration needed[(f)] data gap #1
1013030	Sheep liver	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1013040	Sheep kidney	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1014010	Goat meat	10	10	10	Further consideration needed[(f)] data gap #1
1014020	Goat fat	10	10	10	Further consideration needed [(f)] data gap #1
1014030	Goat liver	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1014040	Goat kidney	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1015010	Horse meat	10	10	10	Further consideration needed[(f)] data gap #1
1015020	Horse fat	10	10	10	Further consideration needed[(f)] data gap #1
1015030	Horse liver	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1

Code number	Commodity	Existing EU MRL (mg/kg)	Existing CXL (mg/kg)	Outcome of the review	
				MRL (mg/kg)	Comment
1015040	Horse kidney	0.7	0.7	0.7	Further consideration needed[(f)] data gap #1
1016010	Poultry meat	0.5	0.5	0.5	Further consideration needed[(c)] data gap #1
1016020	Poultry fat	0.5	0.5	0.5	Further consideration needed[(c)] data gap #1
1016030	Poultry liver	0.1	0.1	0.1	Further consideration needed[(c)] data gap #1
1020010	Cattle milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020020	Sheep milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020030	Goat milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1020040	Horse milk	0.4	0.4	0.4	Further consideration needed[(f)] data gap #1
1030000	Birds' eggs	0.1	0.1	0.1	Further consideration needed[(c)] data gap #1
–	Other commodities of plant and/or animal origin	See Reg. 441/2012	–	–	Further consideration needed[(g)]

MRL: maximum residue level; CXL: codex maximum residue limit.
*: Indicates that the MRL is set at the limit of quantification.
(F): The residue definition is fat soluble.
(a): These CXLs were not legally implemented in the EU, due to different extrapolation rules in line with the EFSA position for the CCPR (EFSA, 2011).
(b): GAP evaluated at EU level is not fully supported by data and a risk to consumers cannot be excluded; CXL is also not sufficiently supported by data and a risk to consumers cannot be excluded. Either a specific LOQ or the default MRL of 0.01 mg/kg may be considered (combination E-IV in Appendix E).
(c): MRL is derived from the existing CXL, which is not sufficiently supported by data but for which no risk to consumers is identified; for apricots, peaches, plums, aubergines, sweet peppers, cucumbers, gherkins, courgettes and broccoli the CXL was recalculated considering the extrapolation rules applicable at EU level in line with the EFSA support for the EU position on the CCPR (EFSA, 2011); there are no relevant authorisations or import tolerances reported at EU level (combination A-V in Appendix E).
(d): 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; existing CXL (recalculated for tomatoes considering the extrapolation rules applicable at EU level in line with the EFSA support for the EU position on the CCPR (EFSA, 2011)) is covered by the tentative MRL (combination F-III in Appendix E).
(e): 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 F-I in Appendix E).
(f): MRL is derived from the existing CXL, which is not sufficiently supported by data but for which no risk to consumers is identified; GAP evaluated at EU level, which is also not fully supported by data, would lead to a lower tentative MRL (combination F-V in Appendix E).
(g): There are no relevant authorisations or import tolerances reported at EU level; no CXL is available or existing CXLs were not legally implemented in the EU legislation since the EU delegation expressed a reservation (EFSA, 2011). 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)

European Food Safety Authority

EFSA PRIMo revision 3.1; 2021/01/06

Novaluron (F)

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

Toxicological reference values

ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	Not necessary
Source of ADI:	EFSA	Source of ARfD:	EFSA
Year of evaluation:	2021	Year of evaluation:	2021

Input values

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

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

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : 2

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

Calculated exposure (% of ADI)	MS Diet	Expsoure (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)
191%	NL toddler	19.12	78%	Milk: Cattle	70%	Apples	30%	Pears		191%
130%	DE child	12.99	81%	Apples	26%	Milk: Cattle	8%	Cherries (sweet)		130%
89%	NL child	8.89	38%	Apples	32%	Milk: Cattle	8%	Pears		89%
69%	UK infant	6.86	50%	Milk: Cattle	10%	Apples	2%	Pears		69%
68%	FR toddler 2 3 yr	6.81	38%	Milk: Cattle	21%	Apples	2%	Pears		68%
54%	FR child 3 15 yr	5.37	30%	Milk: Cattle	11%	Apples	2%	Pears		54%
46%	UK toddler	4.59	27%	Milk: Cattle	11%	Apples	2%	Bovine: Fat tissue		46%
44%	DE women 14-50 yr	4.38	17%	Apples	16%	Milk: Cattle	3%	Cherries (sweet)		44%
44%	DK child	4.37	16%	Milk: Cattle	15%	Apples	5%	Pears		44%
42%	DE general	4.22	16%	Milk: Cattle	16%	Apples	2%	Cherries (sweet)		42%
41%	ES child	4.11	16%	Milk: Cattle	7%	Apples	3%	Chards/beet leaves		41%
38%	FR infant	3.85	22%	Milk: Cattle	11%	Apples	1%	Pears		38%
38%	RO general	3.76	15%	Milk: Cattle	9%	Apples	4%	Tomatoes		38%
35%	GEMS/Food G15	3.53	9%	Milk: Cattle	7%	Apples	5%	Swine: Fat tissue		35%
35%	GEMS/Food G11	3.52	10%	Milk: Cattle	10%	Apples	4%	Swine: Fat tissue		35%
35%	SE general	3.50	16%	Milk: Cattle	7%	Apples	4%	Bovine: Muscle/meat		35%
32%	GEMS/Food G08	3.15	8%	Apples	7%	Milk: Cattle	4%	Swine: Fat tissue		32%
29%	GEMS/Food G06	2.89	8%	Tomatoes	6%	Apples	3%	Milk: Cattle		29%
28%	NL general	2.76	11%	Milk: Cattle	9%	Apples	1%	Pears		28%
28%	GEMS/Food G07	2.76	8%	Milk: Cattle	7%	Apples	2%	Tomatoes		28%
27%	GEMS/Food G10	2.66	7%	Milk: Cattle	5%	Apples	3%	Tomatoes		27%
25%	ES adult	2.51	6%	Milk: Cattle	5%	Apples	3%	Chards/beet leaves		25%
24%	LT adult	2.45	12%	Apples	5%	Milk: Cattle	2%	Swine: Fat tissue		24%
24%	DK adult	2.36	7%	Milk: Cattle	6%	Apples	3%	Swine: Fat tissue		24%
22%	IE adult	2.19	6%	Milk: Cattle	5%	Apples	3%	Pears		22%
21%	PL general	2.09	13%	Apples	2%	Cherries (sweet)	2%	Pears		21%
19%	IT toddler	1.94	6%	Apples	3%	Tomatoes	2%	Chards/beet leaves		19%
18%	FR adult	1.77	6%	Milk: Cattle	5%	Apples	1%	Pears		18%
17%	IT adult	1.72	5%	Apples	3%	Tomatoes	3%	Chards/beet leaves		17%
16%	PT general	1.57	7%	Apples	2%	Pears	2%	Peaches		16%
12%	UK vegetarian	1.18	4%	Milk: Cattle	4%	Apples	1%	Tomatoes		12%
12%	FI 3 yr	1.17	6%	Apples	1%	Tomatoes	1%	Pears		12%
10%	IE child	1.04	5%	Milk: Cattle	2%	Swine: Fat tissue	2%	Apples		10%
10%	UK adult	1.01	4%	Milk: Cattle	3%	Apples	1.0%	Tomatoes		10%
8%	FI 6 yr	0.84	4%	Apples	1%	Pears	1.0%	Tomatoes		8%
6%	FI adult	0.62	4%	Apples	1%	Tomatoes	0.4%	Pears		6%

Conclusion:
The estimated TMDI/NEDI/IEDI was in the range of 0 % to 191.2 % of the ADI.
For 2 diet(s) the ADI is exceeded.
DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.

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

As an ARfD is not necessary/not applicable, no acute risk assessment is performed.

Show results for all crops

Unprocessed commodities

Results for children No. of commodities for which ARfD/ADI is exceeded (IESTI): ---	**Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI): ---
IESTI	**IESTI**
Highest % of ARfD/ADI / Commodities / MRL/input for RA (mg/kg) / Exposure (µg/kg bw)	Highest % of ARfD/ADI / Commodities / MRL/input for RA (mg/kg) / Exposure (µg/kg bw)
Expand/collapse list	
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): ---	**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---
IESTI	**IESTI**
Highest % of ARfD/ADI / Processed commodities / MRL/input for RA (mg/kg) / Exposure (µg/kg bw)	Highest % of ARfD/ADI / Processed commodities / MRL/input for RA (mg/kg) / Exposure (µg/kg bw)
Expand/collapse list	

Conclusion:

European Food Safety Authority

EFSA PRIMo revision 3.1; 2021/01/06

Novaluron (F)

LOQs (mg/kg) range from:	0.01	to:	0.01
Toxicological reference values			
ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	Not necessary
Source of ADI:	EFSA	Source of ARfD:	EFSA
Year of evaluation:	2021	Year of evaluation:	2021

Input values

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

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

Comments:

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	Expsoure (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)
	91%	NL toddler	9.10	78%	Milk: Cattle	2%	Tomatoes	2%	Peaches		91%
	57%	UK infant	5.66	50%	Milk: Cattle	2%	Cherries (sweet)	1.0%	Bovine: Muscle/meat		57%
	45%	FR toddler 2 3 yr	4.53	38%	Milk: Cattle	1%	Beans (with pods)	1%	Tomatoes		45%
	44%	DE child	4.43	26%	Milk: Cattle	8%	Cherries (sweet)	2%	Apricots		44%
	43%	NL child	4.29	32%	Milk: Cattle	2%	Cherries (sweet)	1%	Tomatoes		43%
	41%	FR child 3 15 yr	4.09	30%	Milk: Cattle	2%	Tomatoes	2%	Swine: Fat tissue		41%
	34%	UK toddler	3.35	27%	Milk: Cattle	2%	Bovine: Fat tissue	1%	Tomatoes		34%
	31%	ES child	3.06	16%	Milk: Cattle	3%	Chards/beet leaves	2%	Tomatoes		31%
	28%	RO general	2.75	15%	Milk: Cattle	4%	Tomatoes	3%	Cherries (sweet)		28%
	27%	GEMS/Food G15	2.71	9%	Milk: Cattle	5%	Swine: Fat tissue	3%	Tomatoes		27%
	26%	FR infant	2.63	22%	Milk: Cattle	1%	Chards/beet leaves	0.8%	Beans (with pods)		26%
	26%	DE women 14-50 yr	2.61	16%	Milk: Cattle	3%	Cherries (sweet)	2%	Tomatoes		26%
	26%	SE general	2.58	16%	Milk: Cattle	4%	Bovine: Muscle/meat	2%	Tomatoes		26%
	26%	DE general	2.56	16%	Milk: Cattle	2%	Cherries (sweet)	2%	Swine: Fat tissue		26%
	24%	GEMS/Food G11	2.40	10%	Milk: Cattle	4%	Swine: Fat tissue	2%	Tomatoes		24%
	24%	DK child	2.39	16%	Milk: Cattle	2%	Swine: Muscle/meat	1%	Tomatoes		24%
	23%	GEMS/Food G08	2.27	7%	Milk: Cattle	4%	Swine: Fat tissue	3%	Tomatoes		23%
	22%	GEMS/Food G06	2.23	8%	Tomatoes	3%	Milk: Cattle	2%	Cherries (sweet)		22%
	21%	GEMS/Food G10	2.06	7%	Milk: Cattle	3%	Tomatoes	1%	Bovine: Fat tissue		21%
	20%	GEMS/Food G07	1.99	8%	Milk: Cattle	2%	Tomatoes	1%	Sugar canes		20%
	18%	ES adult	1.79	6%	Milk: Cattle	3%	Chards/beet leaves	2%	Tomatoes		18%
	17%	NL general	1.68	11%	Milk: Cattle	0.9%	Tomatoes	0.8%	Swine: Muscle/meat		17%
	15%	DK adult	1.51	7%	Milk: Cattle	3%	Swine: Fat tissue	1%	Tomatoes		15%
	14%	IE adult	1.42	6%	Milk: Cattle	2%	Peaches	1.0%	Plums		14%
	12%	FR adult	1.17	6%	Milk: Cattle	1%	Tomatoes	0.7%	Peaches		12%
	11%	IT toddler	1.12	3%	Tomatoes	2%	Chards/beet leaves	2%	Peaches		11%
	11%	LT adult	1.12	5%	Milk: Cattle	2%	Swine: Fat tissue	1%	Tomatoes		11%
	10%	IT adult	1.04	3%	Tomatoes	3%	Chards/beet leaves	2%	Peaches		10%
	8%	IE child	0.81	5%	Milk: Cattle	2%	Swine: Fat tissue	0.2%	Sheep: Fat tissue		8%
	7%	UK vegetarian	0.74	4%	Milk: Cattle	1%	Tomatoes	0.3%	Bovine: Fat tissue		7%
	7%	UK adult	0.70	4%	Milk: Cattle	1.0%	Tomatoes	0.5%	Bovine: Muscle/meat		7%
	6%	PT general	0.65	2%	Peaches	2%	Tomatoes	0.8%	Cherries (sweet)		6%
	6%	PL general	0.57	2%	Cherries (sweet)	2%	Tomatoes	0.7%	Plums		6%
	4%	FI 3 yr	0.43	1%	Tomatoes	0.7%	Peaches	0.5%	Strawberries		4%
	3%	FI 6 yr	0.34	1.0%	Tomatoes	0.6%	Peaches	0.4%	Strawberries		3%
	2%	FI adult	0.21	1%	Tomatoes	0.2%	Strawberries	0.2%	Cucumbers		2%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of novaluron (F) is unlikely to present a public health concern.
DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.

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

As an ARfD is not necessary/not applicable, no acute risk assessment is performed.

Show results for all crops

Unprocessed commodities

Results for children No. of commodities for which ARfD/ADI is exceeded (IESTI): ---				**Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
Expand/collapse list							
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): ---				**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
Expand/collapse list							

Conclusion:

European Food Safety Authority

EFSA PRIMo revision 3.1; 2021/01/06

Novaluron (F)

LOQs (mg/kg) range from: to:

Toxicological reference values

ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	Not necessary
Source of ADI:	0.01	Source of ARfD:	
Year of evaluation:	EFSA, 2021	Year of evaluation:	EFSA, 2021

Input values

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

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

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : 2

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)
135%	NL toddler	13.55	75%	Apples	30%	Pears	26%	Milk: Cattle		135%
103%	DE child	10.28	87%	Apples	9%	Milk: Cattle	5%	Pears		103%
62%	NL child	6.23	40%	Apples	11%	Milk: Cattle	8%	Pears		62%
40%	FR toddler 2 3 yr	3.97	22%	Apples	13%	Milk: Cattle	2%	Pears		40%
32%	UK infant	3.20	17%	Milk: Cattle	11%	Apples	2%	Pears		32%
29%	DK child	2.91	16%	Apples	6%	Milk: Cattle	5%	Pears		29%
27%	FR child 3 15 yr	2.74	12%	Apples	10%	Milk: Cattle	2%	Pears		27%
27%	DE women 14-50 yr	2.67	18%	Apples	5%	Milk: Cattle	2%	Tomatoes		27%
25%	UK toddler	2.54	12%	Apples	9%	Milk: Cattle	1%	Bovine: Muscle/meat		25%
25%	DE general	2.54	17%	Apples	5%	Milk: Cattle	1%	Tomatoes		25%
22%	SE general	2.20	7%	Apples	5%	Milk: Cattle	5%	Bovine: Muscle/meat		22%
21%	FR infant	2.09	12%	Apples	7%	Milk: Cattle	1%	Pears		21%
20%	ES child	2.05	8%	Apples	5%	Milk: Cattle	3%	Pears		20%
20%	RO general	2.04	10%	Apples	5%	Milk: Cattle	4%	Tomatoes		20%
19%	GEMS/Food G11	1.89	11%	Apples	3%	Milk: Cattle	2%	Tomatoes		19%
18%	PL general	1.81	14%	Apples	2%	Pears	2%	Tomatoes		18%
17%	LT adult	1.75	13%	Apples	2%	Milk: Cattle	1%	Tomatoes		17%
17%	NL general	1.71	10%	Apples	4%	Milk: Cattle	1%	Pears		17%
17%	GEMS/Food G06	1.70	8%	Tomatoes	6%	Apples	1%	Milk: Cattle		17%
15%	GEMS/Food G15	1.55	8%	Apples	3%	Milk: Cattle	3%	Tomatoes		15%
15%	GEMS/Food G08	1.52	8%	Apples	3%	Tomatoes	2%	Milk: Cattle		15%
15%	GEMS/Food G07	1.51	7%	Apples	3%	Milk: Cattle	2%	Tomatoes		15%
14%	GEMS/Food G10	1.39	5%	Apples	3%	Tomatoes	2%	Milk: Cattle		14%
13%	DK adult	1.33	7%	Apples	2%	Milk: Cattle	2%	Pears		13%
13%	ES adult	1.25	5%	Apples	2%	Pears	2%	Milk: Cattle		13%
12%	IT toddler	1.17	6%	Apples	3%	Tomatoes	2%	Pears		12%
12%	IE adult	1.17	5%	Apples	3%	Pears	2%	Milk: Cattle		12%
12%	PT general	1.16	7%	Apples	2%	Pears	2%	Tomatoes		12%
10%	FR adult	1.02	5%	Apples	2%	Milk: Cattle	1%	Pears		10%
10%	IT adult	0.97	6%	Apples	3%	Tomatoes	2%	Pears		10%
9%	FI 3 yr	0.90	7%	Apples	1%	Tomatoes	1%	Pears		9%
8%	UK vegetarian	0.75	4%	Apples	1%	Milk: Cattle	1%	Tomatoes		8%
6%	UK adult	0.64	3%	Apples	1%	Milk: Cattle	1.0%	Tomatoes		6%
6%	FI 6 yr	0.62	4%	Apples	1%	Pears	1.0%	Tomatoes		6%
6%	FI adult	0.56	4%	Apples	1%	Tomatoes	0.4%	Pears		6%
4%	IE child	0.43	2%	Apples	2%	Milk: Cattle	0.2%	Pears		4%

Conclusion:
The estimated TMDI/NEDI/IEDI was in the range of 0 % to 135.5% of the ADI.
For 2 diet(s), the ADI is exceeded.
DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.

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

As an ARfD is not necessary/not applicable, no acute risk assessment is performed.

Show results for all crops

Unprocessed commodities

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

Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)

Expand/collapse list

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

Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)

Expand/collapse list

Conclusion:

European Food Safety Authority

EFSA PRIMo revision 3.1; 2021/01/06

Novaluron (F)

LOQs (mg/kg) range from: to:

Toxicological reference values

ADI (mg/kg bw per day):	0.01	ARfD (mg/kg bw):	Not necessary
Source of ADI:	0.01	Source of ARfD:	
Year of evaluation:	EFSA, 2021	Year of evaluation:	EFSA, 2021

Input values

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

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

Comments:

Normal mode

Chronic risk assessment: JMPR methodology (IEDI/TMDI)

No of diets exceeding the ADI : ---

	Calculated exposure (% of ADI)	MS Diet	Expsoure (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)	61%	NL toddler	6.05	30%	Pears	26%	Milk: Cattle	2%	Tomatoes		61%
	22%	NL child	2.22	11%	Milk: Cattle	8%	Pears	1%	Tomatoes		22%
	21%	UK infant	2.11	17%	Milk: Cattle	2%	Pears	1%	Bovine: Muscle/meat		21%
	18%	FR toddler 2 3 yr	1.77	13%	Milk: Cattle	2%	Pears	1%	Bovine: Muscle/meat		18%
	16%	DE child	1.61	9%	Milk: Cattle	5%	Pears	2%	Tomatoes		16%
	16%	FR child 3 15 yr	1.57	10%	Milk: Cattle	2%	Pears	2%	Tomatoes		16%
	15%	SE general	1.47	5%	Milk: Cattle	5%	Bovine: Muscle/meat	2%	Pears		15%
	14%	UK toddler	1.36	9%	Milk: Cattle	1%	Bovine: Muscle/meat	1%	Tomatoes		14%
	13%	DK child	1.30	6%	Milk: Cattle	5%	Pears	1%	Bovine: Muscle/meat		13%
	13%	ES child	1.25	5%	Milk: Cattle	3%	Pears	2%	Tomatoes		13%
	11%	RO general	1.06	5%	Milk: Cattle	4%	Tomatoes	0.8%	Pears		11%
	11%	GEMS/Food G06	1.06	8%	Tomatoes	1%	Milk: Cattle	0.6%	Pears		11%
	9%	FR infant	0.92	7%	Milk: Cattle	1%	Pears	0.4%	Bovine: Muscle/meat		9%
	9%	DE women 14-50 yr	0.88	5%	Milk: Cattle	2%	Tomatoes	1.0%	Pears		9%
	9%	GEMS/Food G10	0.86	3%	Tomatoes	2%	Milk: Cattle	1%	Pears		9%
	9%	DE general	0.85	5%	Milk: Cattle	1%	Tomatoes	0.8%	Pears		9%
	8%	GEMS/Food G11	0.80	3%	Milk: Cattle	2%	Tomatoes	1%	Pears		8%
	8%	GEMS/Food G07	0.79	3%	Milk: Cattle	2%	Tomatoes	1%	Pears		8%
	8%	GEMS/Food G15	0.79	3%	Milk: Cattle	3%	Tomatoes	1%	Pears		8%
	7%	ES adult	0.72	2%	Pears	2%	Milk: Cattle	2%	Tomatoes		7%
	7%	NL general	0.70	4%	Milk: Cattle	1%	Pears	0.9%	Tomatoes		7%
	7%	GEMS/Food G08	0.68	3%	Tomatoes	2%	Milk: Cattle	1.0%	Pears		7%
	7%	IE adult	0.68	3%	Pears	2%	Milk: Cattle	0.9%	Tomatoes		7%
	7%	DK adult	0.67	2%	Milk: Cattle	2%	Pears	1%	Tomatoes		7%
	6%	IT toddler	0.56	3%	Tomatoes	2%	Pears	0.0%	Blueberries		6%
	5%	FR adult	0.49	2%	Milk: Cattle	1%	Pears	1%	Tomatoes		5%
	5%	LT adult	0.45	2%	Milk: Cattle	1%	Tomatoes	1%	Pears		5%
	4%	PT general	0.43	2%	Pears	2%	Tomatoes				4%
	4%	IT adult	0.42	3%	Tomatoes	2%	Pears	0.0%	Blueberries		4%
	4%	PL general	0.39	2%	Pears	2%	Tomatoes	0.1%	Blueberries		4%
	4%	UK adult	0.36	1%	Milk: Cattle	1.0%	Tomatoes	0.7%	Bovine: Muscle/meat		4%
	3%	UK vegetarian	0.34	1%	Milk: Cattle	1%	Tomatoes	0.5%	Pears		3%
	2%	FI 3 yr	0.25	1%	Tomatoes	1%	Pears				2%
	2%	FI 6 yr	0.22	1%	Pears	1.0%	Tomatoes				2%
	2%	IE child	0.20	2%	Milk: Cattle	0.2%	Pears	0.1%	Tomatoes		2%
	2%	FI adult	0.16	1%	Tomatoes	0.4%	Pears				2%

Conclusion:
The estimated long-term dietary intake (TMDI/NEDI/IEDI) was below the ADI.
The long-term intake of residues of novaluron (F) is unlikely to present a public health concern.
DISCLAIMER: Dietary data from the UK were included in PRIMO when the UK was a member of the European Union.

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

As an ARfD is not necessary/not applicable, no acute risk assessment is performed.

Show results for all crops

Unprocessed commodities

Results for children No. of commodities for which ARfD/ADI is exceeded (IESTI): ---				**Results for adults** No. of commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
Expand/collapse list							
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): ---				**Results for adults** No of processed commodities for which ARfD/ADI is exceeded (IESTI): ---			
IESTI				**IESTI**			
Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)	Highest % of ARfD/ADI	Processed commodities	MRL/input for RA (mg/kg)	Exposure (µg/kg bw)
Expand/collapse list							

Conclusion:

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: novaluron				
Apple, pomace, wet	3.06	STMR × PF (4.4)	3.06	STMR × PF (4.4)
Cotton, undelinted seed	0.06	STMR	0.06	STMR
Cotton, meal	0.04	STMR × PF (0.6)	0.04	STMR × PF (0.6)

STMR: supervised trials median residue; PF: processing factor.

D.2. Consumer risk assessment without consideration of the existing CXLs

Commodity	Chronic risk assessment	
	Input value (mg/kg)	Comment
Risk assessment residue definition: novaluron		
Apples	0.70	Scenario EU 1: STMR (tentative)
	–	Scenario EU 2: no fall-back available
Pears	0.70	STMR (tentative)
Blueberries	1.72	STMR (tentative)
Cranberries	1.72	STMR (tentative)
Tomatoes	0.22	STMR (tentative)
Cotton seeds	0.06	STMR (tentative)
Bovine and equine meat	0.11	0.8 × STMR muscle + 0.2 × STMR fat (tentative)
Bovine and equine fat	0.43	STMR (tentative)
Bovine and equine liver	0.05	STMR (tentative)
Bovine and equine kidney	0.05	STMR (tentative)
Sheep and goat meat	0.10	0.8 × STMR muscle + 0.2 × STMR fat (tentative)
Sheep and goat fat	0.38	STMR (tentative)
Sheep and goat liver	0.05	STMR (tentative)
Sheep and goat kidney	0.05	STMR (tentative)
Cattle and horse milk	0.04	STMR (tentative)
Sheep and goat milk	0.04	STMR (tentative)

STMR: supervised trials median residue.

D.3. Consumer risk assessment with consideration of the existing CXLs

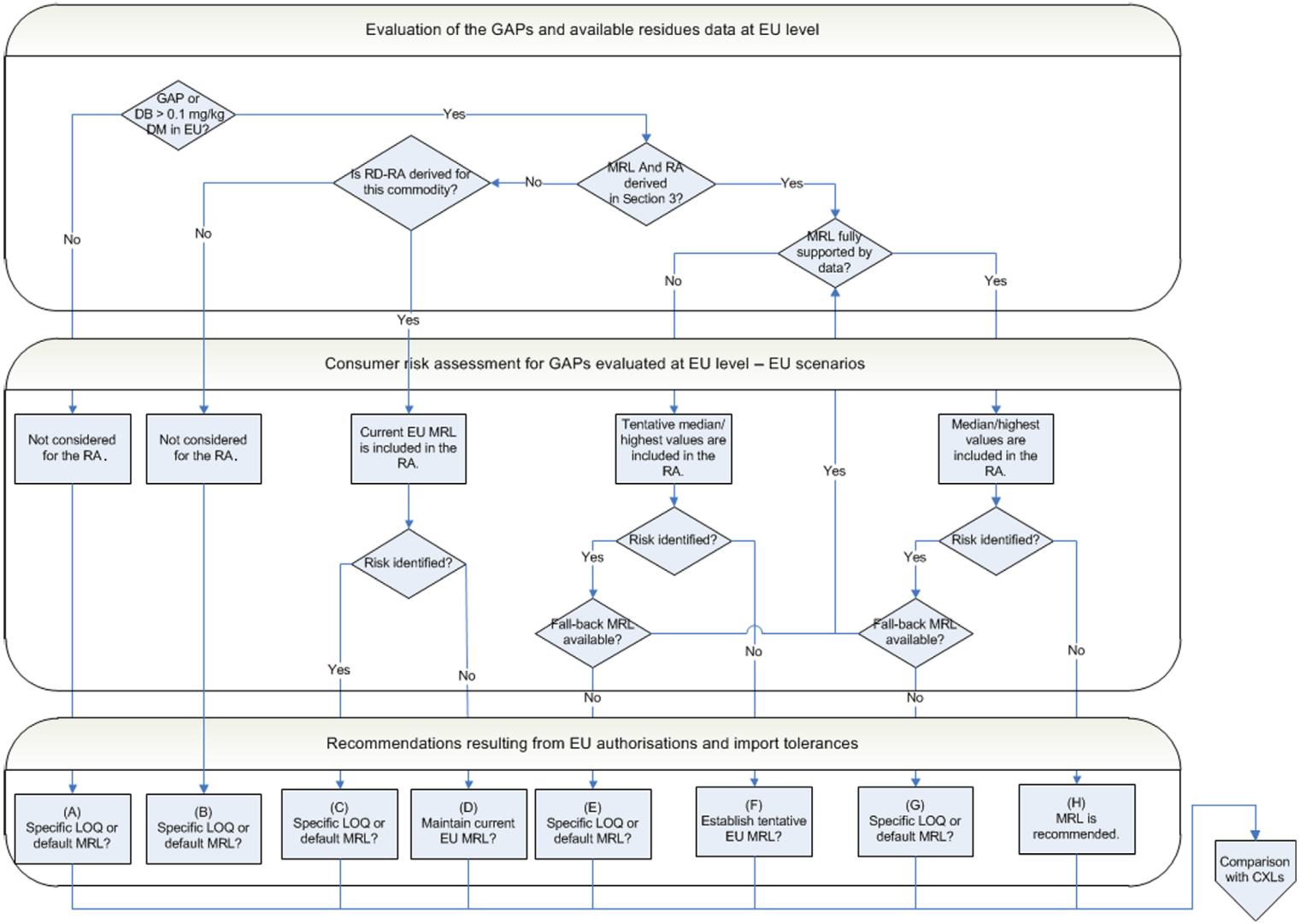
Commodity	Chronic risk assessment	
	Input value (mg/kg)	Comment
Risk assessment residue definition: novaluron		
Apples	0.65	Scenario CX 1: STMR (CXL) (tentative)
	–	Scenario CX 2: no fall-back available
Pears	0.70	Scenario CX 1: STMR (tentative)
	–	Scenario CX 2: no fall-back available
Quinces	0.65	STMR (CXL) (tentative)

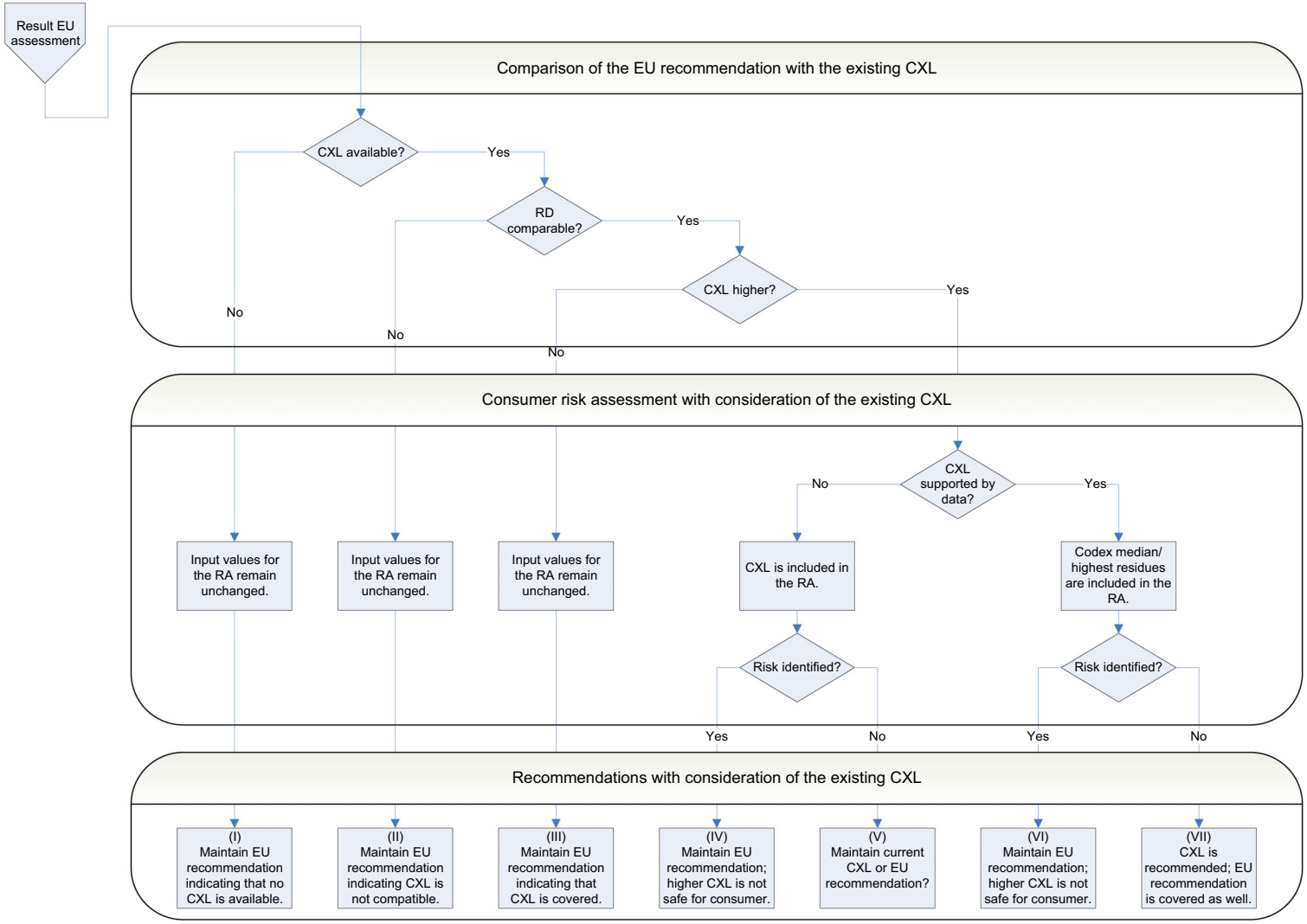
Commodity	Chronic risk assessment	
	Input value (mg/kg)	Comment
Medlar	0.65	STMR (CXL) (tentative)
Loquat	0.65	STMR (CXL) (tentative)
Apricots	0.58	STMR (CXL) (tentative)
Cherries	2.20	STMR (CXL) (tentative)
Peaches	0.58	STMR (CXL) (tentative)
Plums	0.41	STMR (CXL) (tentative)
Strawberries	0.15	STMR (CXL) (tentative)
Blueberries	1.72	STMR (CXL) (tentative)
Cranberries	1.72	STMR (CXL) (tentative)
Potatoes	0.01*	STMR (CXL) (tentative)
Tomatoes	0.22	STMR (tentative)
Peppers	0.07	STMR (CXL) (tentative)
Aubergines (egg plants)	0.10	STMR (CXL) (tentative)
Cucumbers	0.05	STMR (CXL) (tentative)
Gherkins	0.05	STMR (CXL) (tentative)
Courgettes	0.05	STMR (CXL) (tentative)
Melons	0.05	STMR (CXL) (tentative)
Pumpkins	0.05	STMR (CXL) (tentative)
Watermelons	0.05	STMR (CXL) (tentative)
Broccoli	0.11	STMR (CXL) (tentative)
Red mustard	3.60	STMR (CXL) (tentative)
Beet leaves (chard)	4.0	STMR (CXL) (tentative)
Beans (fresh, with pods)	0.17	STMR (CXL) (tentative)
Beans (fresh, without pods)	0.17	STMR (CXL) (tentative)
Beans (dry)	0.05	STMR (CXL) (tentative)
Soya bean	0.01*	STMR (CXL) (tentative)
Cotton seeds	0.06	STMR (tentative)
Sugar cane	0.08	STMR (CXL) (tentative)
Swine muscle	0.08	0.8 × STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Swine fat tissue	1.70	STMR (CXL) (tentative)
Swine liver	0.13	STMR (CXL) (tentative)
Swine kidney	0.13	STMR (CXL) (tentative)
Bovine muscle	0.08	0.8 x STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Bovine fat tissue	1.70	STMR (CXL) (tentative)
Bovine liver	0.13	STMR (CXL) (tentative)
Bovine kidney	0.13	STMR (CXL) (tentative)
Sheep muscle	0.08	0.8 × STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Sheep fat tissue	1.70	STMR (CXL) (tentative)
Sheep liver	0.13	STMR (CXL) (tentative)
Sheep kidney	0.13	STMR (CXL) (tentative)
Goat muscle	0.08	0.8 × STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Goat fat tissue	1.70	STMR (CXL) (tentative)
Goat liver	0.13	STMR (CXL) (tentative)
Goat kidney	0.13	STMR (CXL) (tentative)

Commodity	Chronic risk assessment	
	Input value (mg/kg)	Comment
Equine muscle	0.08	0.8 × STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Equine fat tissue	1.70	STMR (CXL) (tentative)
Equine liver	0.13	STMR (CXL) (tentative)
Equine kidney	0.13	STMR (CXL) (tentative)
Poultry muscle	0.01	0.8 × STMR (CXL) muscle + 0.2 × STMR (CXL) fat (tentative)
Poultry fat tissue	0.13	STMR (CXL) (tentative)
Poultry liver	0.02	STMR (CXL) (tentative)
Cattle milk	0.13	STMR (CXL) (tentative)
Sheep milk	0.13	STMR (CXL) (tentative)
Goat milk	0.13	STMR (CXL) (tentative)
Horse milk	0.13	STMR (CXL) (tentative)
Birds eggs	0.03	STMR (CXL) (tentative)

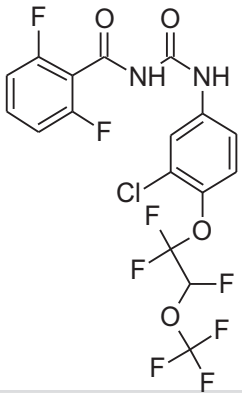
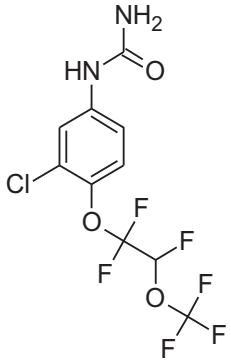
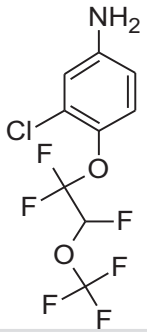
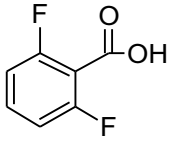
STMR: supervised trials median residue; CXL: codex maximum residue limit.
*: Indicates that the MRL is set at the limit of quantification.

Appendix E – Decision tree for deriving MRL recommendations




Result EU assessment
Comparison of the EU recommendation with the existing CXL
CXL available?
Yes
No
RD comparable?
Yes
No
CXL higher?
Yes
No
Consumer risk assessment with consideration of the existing CXL
CXL supported by data?
No
Yes
Input values for the RA remain unchanged.
Input values for the RA remain unchanged.
Input values for the RA remain unchanged.
CXL is included in the RA.
Codex median/ highest residues are included in the RA.
Risk identified?
Risk identified?
Yes
No
Yes
No
Recommendations with consideration of the existing CXL
(I) Maintain EU recommendation indicating that no CXL is available.
(II) Maintain EU recommendation indicating CXL is not compatible.
(III) Maintain EU recommendation indicating that CXL is covered.
(IV) Maintain EU recommendation; higher CXL is not safe for consumer.
(V) Maintain current CXL or EU recommendation?
(VI) Maintain EU recommendation; higher CXL is not safe for consumer.
(VII) CXL is recommended; EU recommendation is covered as well.

Appendix F – Used compound codes

Code/trivial name	IUPAC name/SMILES notation/InChiKey[a]	Structural formula[b]
Novaluron	*N*-({3-chloro-4-[(2*RS*)-1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl}carbamoyl)-2,6-difluorobenzamide Clc1cc(ccc1OC(F)(F)C(F)OC(F)(F)F)NC(=O)NC(=O)c1c(F)cccc1F NJPPVKZQTLUDBO-UHFFFAOYSA-N	
Metabolite 275-352-I	1-{3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl}urea KEVRTKYDPZZPIA-UHFFFAOYSA-N Clc1cc(ccc1OC(F)(F)C(F)OC(F)(F)F)NC(N)=O	
Metabolite 275-309-I	3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]aniline DUQYSTOFYBWCDV-UHFFFAOYSA-N Clc1cc(N)ccc1OC(F)(F)C(F)OC(F)(F)F	
Metabolite 275-158-I	2,6-difluorobenzoic acid ONOTYLMNTZNAQZ-UHFFFAOYSA-N OC(=O)c1c(F)cccc1F	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): ACD/Name 2019.1.1 ACD/Labs 2019 Release (File version N05E41, Build 110555, 18 July 2019).
(b): ACD/ChemSketch 2019.1.1 ACD/Labs 2019 Release (File version C05H41, Build 110712, 24 July 2019).