Updated peer review of the pesticide risk assessment of the active substance flumioxazin

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Abstract

The conclusions of the EFSA following the peer review of the initial risk assessments carried out by the competent authority of the rapporteur Member State, the Czech Republic, for the pesticide active substance flumioxazin are reported. The context of the peer review was that required by Commission Regulation (EU) No 1141/2010 as amended by Commission Implementing Regulation (EU) No 380/2013. The conclusions were reached on the basis of the evaluation of the representative uses of flumioxazin as a herbicide on winter wheat and sunflower (pre- and post-emergence). The conclusions were updated with regard to the endocrine-disrupting properties. The reliable end points concluded as being appropriate for use in regulatory risk assessment, derived from the available studies and literature in the dossier peer reviewed, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

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Summary

Commission Regulation (EU) No 1141/2010, as amended by Commission Implementing Regulation (EU) No 380/2013 (hereinafter referred to as ‘the Regulation’), lays down the procedure for the renewal of the approval of a second group of active substances in Annex I to Council Directive 91/414/EEC and establishes the list of those substances. Flumioxazin is one of the active substances listed in the Regulation.

The rapporteur Member State (RMS) provided its initial evaluation of the dossier on flumioxazin in the Renewal Assessment Report (RAR), which was received by the European Food Safety Authority (EFSA) on 4 March 2013. The peer review was initiated on 18 March 2013 by dispatching the RAR for consultation of the Member States and the applicant Sumitomo Chemical Agro Europe S.A.S.

Following consideration of the comments received on the RAR, it was concluded that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology, and that EFSA should adopt a conclusion on whether flumioxazin can be expected to meet the conditions provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and the Council.

The conclusions laid down in this report were reached on the basis of the evaluation of the representative uses of flumioxazin as a herbicide on winter wheat, sunflower (pre-emergence) and sunflower (post-emergence), as proposed by the applicant. Full details of the representative uses can be found in Appendix A to this report.

In the area of identity, physical/chemical/technical properties and methods of analysis, a data gap was identified for a method of analysis for a metabolite in surface water and for independent laboratory validation (ILV) for the QuEChERS method acidic matrix.

In the area of mammalian toxicology several data gaps, issues that could not be finalised and critical area of concerns were identified. Insufficient information was available to address whether the toxicity studies were representative of the proposed technical specification for the active substance and associated impurities, leading to a critical area of concern. Insufficient information was available to assess the toxicological relevance of impurities.

With respect to residues and consumer safety, no critical areas of concern were identified. However, data gaps were identified for residue trials in sunflower in SEU, and for addressing the potential for residues in rotational crops.

No critical areas of concern were identified with respect to the environmental exposure to residues of flumioxazin or its metabolites with the available information. However, a data gap has been identified for reliable adsorption data of flumioxazin in at least an additional soil to complete the data set and overcome the limitations of the available study. Therefore, the ground water exposure assessment is not finalised.

With respect to ecotoxicology, some data gaps were identified.

The assessment of the endocrine-disrupting properties of flumioxazin for humans and non-target organisms could not be finalised due to the incomplete data sets. A conclusion on whether the criteria for endocrine disruption for both humans and non-target organisms through EATS-modalities as set in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be reached due to the incomplete data sets.
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Background

Commission Regulation (EU) No 1141/2010\(^1\) (hereinafter referred to as ‘the Regulation’) as amended by Commission Implementing Regulation (EU) No 380/2013\(^2\) lays down the detailed rules for the procedure of the renewal of the approval of a second group of active substances. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States and the applicant for comments on the initial evaluation in the Renewal Assessment Report (RAR) provided by the rapporteur Member State (RMS), and the organisation of an expert consultation, where appropriate.

In accordance with Article 16 of the Regulation, if mandated, EFSA is required to adopt a conclusion on whether the active substance is expected to meet the conditions provided for in Article 4 of Regulation (EC) No 1107/2009 within 6 months from the receipt of the mandate, subject to an extension of up to 9 months where additional information is required to be submitted by the applicant (s) in accordance with Article 16(3).

In accordance with Article 4 of the Regulation the Czech Republic (hereinafter referred to as the ‘RMS’) received an application from Sumitomo Chemical Agro Europe S.A.S. for the renewal of approval of the active substance flumioxazin. Complying with Article 11 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on flumioxazin in the RAR, which was received by the EFSA on 4 March 2013 (Czech Republic, 2013). The peer review was initiated on 18 March 2013 by dispatching the RAR to Member States and the applicant Sumitomo Chemical Agro Europe S.A.S. for consultation and comments. In addition, the EFSA conducted a public consultation on the RAR. The comments received were collated by the EFSA and forwarded to the RMS for compilation and evaluation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant’s response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 16(3) of the Regulation were considered in a telephone conference between the EFSA, the RMS, ECHA and the European Commission on 12 August 2013. On the basis of the comments received, the applicant’s response to the comments and the RMS’s evaluation thereof it was concluded that additional information should be requested from the applicant and that the EFSA should organise an expert consultation in the areas of mammalian toxicology, residues and ecotoxicology. According to Article 16(2) of the Regulation, COM decided to consult the EFSA. The mandate was received on 2 September 2013.

The outcome of the telephone conference, together with EFSA’s further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, and the additional information to be submitted by the applicant, were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table, together with the outcome of the expert consultation where this took place, were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in May 2014.

Commission Regulation (EU) 2018/605 introduced new scientific criteria for the determination of endocrine-disrupting (ED) properties, applicable as of 10 November 2018 to all applications for the approval/renewal of active substances, including pending applications. The peer review on the active substance flumioxazin was already completed at the time of entry into force of the new criteria, and an assessment of the ED potential in line with the ECHA and EFSA (2018) guidance document\(^3\) for this substance was not available.

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\(^1\) Commission Regulation (EU) No 1141/2010 of 7 December 2010 laying down the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC and establishing the list of those substances. OJ L 116, 26.4.2013, p. 4.

\(^2\) Commission Implementing Regulation (EU) No 380/2013 of 25 April 2013 amending Regulation (EU) No 1141/2010 as regards the submission of the supplementary complete dossier to the Authority, the other Member States and the Commission. OJ L 322, 8.12.2011, p. 10-19.

\(^3\) ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC), Anderson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A and Van der Linden S. 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(4):5311, 135 pp. https://doi.org/10.2903/j.efsa.2018.5311. ECHA-18-G-01-EN.
Since on the basis of the EFSA Conclusion published on 4 June 2014, it was not possible for risk managers to conclude whether or not the active substance flumioxazin is an endocrine disruptor, the European Commission requested EFSA to re-assess the information in accordance with the new criteria. Flumioxazin is a substance covered by the second stage of the renewal programme (AIR II) in accordance with Regulation (EU) No 1141/2010, and therefore, it is not covered by the scope of Regulation 2018/1659\(^4\) (amendment of 844/2012\(^5\) ). Following a specific mandate received from the Commission in December 2019, taking into account the dossier submitted for the renewal of approval and any new data evaluated by ECHA for the latest opinion adopted by the ECHA Committee for Risk assessment (RAC), EFSA has conducted an assessment of the endocrine-disrupting properties of the active substance flumioxazin in line with the ECHA and EFSA (2018) in order to decide whether flumioxazin meets the new scientific criteria on endocrine-disrupting properties in line with Commission Regulation (EU) 2018/605.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the representative uses as a herbicide on winter wheat, sunflower (pre-emergence) and sunflower (post-emergence), as proposed by the applicant. The conclusions were updated with regard to the endocrine-disrupting properties. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The Peer Review Report (EFSA, 2014, 2020a) comprises the following documents, in which all views expressed during the course of the peer review, including minority views, can be found:

- the comments received on the RAR,
- the Reporting Table (12 August 2013),
- the Evaluation Table (3 June 2014, updated 6 August 2020),
- the reports of the scientific consultation with Member State experts (where relevant),
- the comments received on the assessment of the additional information (where relevant),
- the comments received on the EFSA addendum on endocrine assessment,
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR including its addendum (compiled version of March 2014 containing all individually submitted addenda (Czech Republic, 2014)), the Peer Review Report and the EFSA addendum on endocrine assessment (EFSA, 2020b), all these documents are considered as background documents to this conclusion.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the EU for which the applicant has not demonstrated to have regulatory access to the information on which this conclusion report is based.

### The active substance and the formulated product

Flumioxazin is the ISO common name for \(N\)-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2H-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboximide (IUPAC).

The representative formulated product for the evaluation was ‘Flumioxazin 50WP’ a wettable powder formulation containing 500 g/kg flumioxazin.

The representative uses were outdoor foliar sprays for the control of weeds in winter wheat and sunflower (pre- and post-emergence). Full details of the good agricultural practice (GAP) can be found in the list of end points in Appendix A.

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\(^4\) Commission Implementing Regulation (EU) No 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine-disrupting properties introduced by Regulation (EU) 2018/605.

\(^5\) Commission Implementing Regulation (EU) No 844/2012 of 18 September 2012 setting out the provisions necessary for the implementation of the renewal procedure for active substances, as provided for in Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. OJ L 252, 19.9.2012, p. 26–32.
Conclusions of the evaluation

1. **Identity, physical/chemical/technical properties and methods of analysis**

   The following guidance documents were followed in the production of this conclusion: SANCO/3030/99 rev.4 (European Commission, 2000), Sanco/10597/2003 – rev. 10.1 (European Commission, 2012) and SANCO/825/00 rev. 8.1 (European Commission, 2010).

   The minimum purity of the active substance as manufactured is 96%. It is currently not known if the technical material contains relevant impurities (see Section 2).

   The main data regarding the identity of flumioxazin and its physical and chemical properties are given in Appendix A.

   The compounds in the residue definition for plants can be determined with a multi-residue method (DFG S19) and Quick, Easy, Cheap, Effective, Rugged and Safe analytical method (QuEChERS). However, independent laboratory validation (ILV) for the QuEChERS method acidic matrix is identified as a data gap. Analytical methods for food of animal origin are not required as there is no intake by livestock. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods are available to monitor the compounds in the residue definitions for soil and water; however, there is a data gap for a method for the metabolite 482-HA in surface water. A liquid chromatography–mass spectrometry (LC-MS) method is available for air. A method for body fluids and tissues is not required as the active substance is not considered as toxic or very toxic.

2. **Mammalian toxicity**

   Flumioxazin was discussed at the Pesticides Peer Review Experts’ Meeting 109 in January 2014 and assessed based on the following guidance documents: SANCO/221/2000 – rev. 10-final (European Commission, 2003), SANCO/10597/2003 – rev. 10.1 (European Commission, 2012) and EFPSA PPR Panel (2012).

   To assess the toxicological profile of flumioxazin, the applicant submitted a set of valid toxicity studies. However, insufficient information was available to address whether the toxicity studies were representative of the proposed technical specification for the active substance and associated impurities (see Section 1) leading to a critical area of concern. For impurities, the applicant did not provide sufficient information to exclude their relevance from the toxicological point of view.

   Toxicity studies included the toxicokinetics, acute and short-term toxicity, genotoxicity, long-term and reproductive toxicity studies that were already included in the original 1994 dossier as well as new studies (i.e. genotoxicity study, neurotoxicity studies and additional mechanistic data). The toxicity studies allowed the setting of reference values for the active substance. Consumer (see Section 3) and non-consumer exposure estimates according to the supported uses in sunflower and winter wheat were then compared to the reference values to assess the risk to flumioxazin in the product ‘Flumioxazin 50 WP’.

   In the toxicokinetics studies, the substance was extensively and rapidly absorbed. Oral absorption was estimated to be greater than 80%. There was no evidence for accumulation. Excretion of substance was predominantly through the faecal route but with appreciable amounts excreted in urine. The major metabolites are sulfonate derivatives in faeces and sulfonate alcohol and acetanilide derivatives in urine.

   In the acute toxicity studies, the substance has low acute toxicity when administered orally, dermally or by inhalation to rats. It is not a skin or eye irritant or a dermal sensitiser.

   In short-term oral toxicity studies with rats, mice and dogs, the critical effects included anaemia in rats and liver toxicity effects in all species. The rat was the most sensitive species.

   Based on the available genotoxicity studies, the substance is unlikely to be genotoxic.

   In long-term studies with rats and mice, the critical effects included anaemia and chronic nephropathy in rats and liver toxicity effects in mice. The rat was again the most sensitive species. The substance showed no carcinogenic potential in both species.

   Reproductive toxicity studies included a two-generation toxicity study in rats, developmental toxicity studies in rats and rabbits and mechanistic data.

   In the two-generation toxicity study, the substance produced toxic effects in adults i.e. effects on clinical appearance, reduced body weight and reduced weight of testes and epididymis, brain and
prostate at higher dose levels than those producing toxic effects in offspring i.e. reduced pup weight, stillbirths and consequentially reduction in live born pups.

In the developmental toxicity studies, developmental effects were observed in rats but not in rabbits at dose levels where no toxicity was observed in the dams. The developmental effects observed in rats consisted of increases in the incidence of ventricular septal defects, wavy ribs, curvature of the scapula and decreased ossification of sacrococcygeal vertebral bodies. The applicant submitted additional mechanistic data to support the proposed mode of action (MOA) by which flumioxazin would cause developmental toxicity in rats and to exclude the human relevance of these developmental effects. The proposed MOA would be the inhibition of the enzyme protoporphyrinogen oxidase (PPO) interfering with normal haem synthesis and resulting in anaemia. This condition would lead to hypoxia in fetal tissues followed by impairment of other liver functions including protein synthesis and ultimately fetal oedema and anaemia. Concurrently, the fetus would compensate for the anaemia by pumping a greater volume of blood leading to the observed enlargement of the heart. The acceptability of the additional mechanistic data and the different sensitivity humans/rats to PPO inhibition was discussed at the Pesticides Peer Review Experts’ Meeting 109: the experts considered the proposed mechanism for flumioxazin-induced developmental toxicity via inhibition of PPO plausible, but the experts could not clearly exclude other mechanisms. Based on available information, the experts did not exclude the relevance of the proposed mechanism to humans and proposed to keep the current harmonised classification and labelling, in accordance with the provisions of Regulation (EC) No 1272/2008, of flumioxazin as toxic for reproduction category 1B, leading to a critical area of concern with regard to the approval criteria of Annex II, Point 3.6.4 of Regulation (EC) No 1107/2009.

A RAC opinion was recently published (ECHA, 2019), where the putative MoA namely inhibition of protoporphyrinogen oxidase/PPO was discussed, which led to the RAC-modified classification as Repro. 2, H361d (for developmental toxicity in rats).

The substance did not show a neurotoxic potential in acute and short-term neurotoxicity studies in rats.

Concerning the setting of references values, the agreed acceptable daily intake (ADI) is 0.018 mg/kg body weight (bw) per day, on the basis of the relevant long-term no observed adverse effect level (NOAEL) of 1.8 mg/kg bw in the 2-year study in rats based on anaemia and chronic nephropathy at 18 mg/kg bw per day. An uncertainty factor of 100 was applied. The ADI provides a margin of exposure of at least 1,000 relative to the lowest observable adverse effect level (LOAEL) for developmental effects in rats.

The agreed acute reference dose (ARfD) is 0.10 mg/kg bw based on the NOAEL of 10 mg/kg bw per day for developmental effects observed at 30 mg/kg bw per day in the developmental toxicity study in rats. An uncertainty factor of 100 was applied. The ARfD provides a margin of exposure of 300 relative to the LOAEL for developmental effects in rats.

The agreed systemic acceptable operator exposure level (AOEL) is 0.022 mg/kg bw per day on the basis of the relevant short-term NOAEL of 2.2 mg/kg bw per day in the 90-day study in rats based on anaemia and liver toxicity effects at 22.4 mg/kg bw per day. An uncertainty factor of 100 was applied. No correction for oral absorption is needed to derive the AOEL. The AOEL provides a margin of exposure of at least 1000 relative to the LOAEL for developmental effects in rats.

The RMS estimated non-consumer exposure (i.e. operator, worker, bystander and resident) using dermal absorption values of flumioxazin in ‘Flumioxazin 50 WP’ of 2.8% for the concentrate and of 18.5% for the dilution as input values. The RMS considered the representative use in sunflowers as a worst-case scenario compared to winter wheat. The estimated operator exposure was below the AOEL (25% of the AOEL) without the use of personal protective equipment (PPE) according to the German Model. Worker exposure was below the AOEL even without the use of PPE (10.5% of the AOEL). Bystander and resident exposure was below the AOEL (maximum 2.37% of the AOEL; children, resident).

3. Residues

The assessment in the residue section is based on the guidance documents listed in the document 1607/VI/97 rev.2 (European Commission, 1999), and the JMPR recommendations on livestock burden calculations stated in the 2004 and 2007 JMPR reports (JMPR, 2004, 2007).

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6 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 OJ L 353, 31.12.2008, p. 1–1355.
Primary crop metabolism of flumioxazin was investigated following application on fruits (apples, grapes) and on pulses and oilseeds (peanuts, soya bean). Metabolism following foliar application on sugar cane was also investigated. While identification of residues was not obtained in apple, soya bean and grapes, a different metabolic pattern of flumioxazin was observed in peanuts after soil treatment compared to cereals after foliar treatment, suggesting that the metabolic picture is mainly driven by the metabolism/degradation of the parent compound in soil.

As for the representative uses, low levels of residues are expected, and it was decided to propose flumioxazin only as the residues definition for monitoring and risk assessment in all commodities of plant origin based on the post- and pre-emergence metabolism data, using expert judgement.

The representative uses in wheat and in sunflower in the NEU are supported by a sufficient number of supervised residue trials, which allowed an estimation of the expected residue concentrations in the relevant crops and to derive MRL proposals. Sufficient freezer storage stability of the residues determined in the residue trials was demonstrated. Residue trial data were insufficient for the representative use in sunflower in SEU (data gap). Significant residues of flumioxazin are not expected in processed commodities. Therefore, the investigation of the effect of industrial and/or household processing on the nature and the level of residues was not required.

To assess the requirement for investigation of residues including soil metabolites in rotational crops, a case has been made by the applicant for waiving such data; however, the case has not been officially evaluated by the RMS and a data gap was identified.

As for the representative uses, the estimated dietary burden for livestock was below the trigger value for requiring data in food-producing animals, and therefore, no further assessment was conducted concerning residues in food of animal origin. It is noted that metabolism data are available in goats and laying hens.

Chronic and acute consumer exposure resulting from the representative uses in NEU in the framework of the peer review was calculated using EFSA PRIMo rev.2. The highest chronic exposure represented 1% of the ADI (WHO cluster B) and the acute exposure was calculated for wheat and sunflower, both representing less than 1% of the ARfD.

4. Environmental fate and behaviour

If not otherwise indicated, fate and behaviour studies considered during the peer review were already presented in the original 1994 dossier. The studies are still considered acceptable and no new studies have been submitted in the updated dossier. However, kinetic parameters have been re-evaluated to the current guidelines (FOCUS, 2006).

The route and rate of degradation of flumioxazin under aerobic conditions were investigated in four soils at 20°C, two soils at 25°C and one soil at 10°C with [Ph-14C] and [THP-14C]-labelled compound. Flumioxazin exhibits moderate persistence in these studies. Two metabolites corresponding to a diacid and a cyclic anhydride in equilibrium, THPA and Δ1-TPA, were observed above 5% AR in two or more consecutive sampling data points during the course of the studies. This pair of metabolites exhibited low persistence in the soil where data were kinetically assessed. Unextracted residues at the end of the studies (120 days) amounted to a maximum of 73.9% AR ([Ph-14C] labelled). Mineralisation (as CO2) was up to 13.5% AR for the [Ph-14C]-labelled flumioxazin and up to 54.9% AR for the [THP-14C]-labelled flumioxazin. A new rate of degradation study of 14C-THPA metabolite in three soils under aerobic conditions has been presented in the updated dossier. THPA exhibits very low to low persistence in these experiments.

Degradation of flumioxazin in soil under anaerobic conditions was investigated in one soil. Flumioxazin also exhibited moderate persistence under these conditions and no major metabolite was identified. Photolysis in soil of [Ph-14C]-labelled and [THP-14C]-labelled flumioxazin was investigated in experiments under simulated summer sunlight for 6 and 14 days of 12 h irradiation cycles. Flumioxazin degraded more rapidly on irradiated soil than on dark soil. In the irradiated [THP-14C]-labelled experiment metabolites, THPA and Δ1-TPA exceeded 10% AR in one sampling date (12.9% AR and 21.6% AR, respectively). Although not triggered, a field dissipation study in two vine fields in France is available. Results with respect to the persistence of flumioxazin are in line with what was observed in the laboratory studies.

PEC soil were calculated for flumioxazin and major soil photolysis metabolites THPA and Δ1-TPA for the representative uses in winter wheat and sunflower using worst-case half-lives and assuming 100% formation for metabolite THPA and 21.6% formation for metabolite Δ1-TPA.
The mobility of flumioxazin was assessed by determination of adsorption coefficient by high-performance liquid chromatography and batch adsorption/desorption studies in three soils. Only a concentration was used in the adsorption soil experiments (Freudlich adsorption isotherms were not determined). In the RMS assessment presented in the RAR and during the peer review, the serious limitations of the old study were considered and the need for at least experiments in an additional soil to complete the data set was identified. Therefore, a data gap was identified by the RMS and confirmed during the peer review for an additional soil adsorption study. Available data indicate that flumioxazin may be considered to exhibit low mobility in soil. Current surface and ground water exposure assessment would need to be confirmed once a complete soil adsorption data set becomes available. A new soil adsorption/desorption study with metabolite THPA in five soils (and one sediment) has been submitted in the updated dossier. According this study, THPA may be considered medium to very highly mobile. A high-performance liquid chromatography (HPLC) method was used to estimate the soil adsorption of the metabolite Δ1-TPA that is assumed to be in equilibrium with THPA in the presence of moisture. This estimation indicated that Δ1-TPA would be expected to exhibit high mobility in soil. An additional soil adsorption/desorption study is available for the APF metabolite in four soils. This metabolite may be considered to exhibit medium to low mobility in soil. Column leaching and aged column leaching test are available in the old dossier but not used in current assessment to derive any quantitative parameter.

Flumioxazin is rapidly hydrolysed in buffer aqueous solutions (25°C, pH 5, 7 and 9). Hydrolysis is faster at alkaline pH. Major hydrolysis metabolites are THPA, (pH 5 and pH 7), APF (pH 5 and pH 7 and 482-HA (pH 7 and pH 9)). Flumioxazin degradation is enhanced by aqueous photolysis; metabolite 482-PHO is formed at high levels in the irradiated experiment (max. 74.6% AR). Flumioxazin was not readily biodegradable according to the OECD 301B test study submitted in the updated dossier. The degradation of flumioxazin was investigated under dark (aerobic and anaerobic) and irradiated aerobic water/sediment systems (the irradiated system was investigated in a peer reviewed scientific paper submitted in the updated dossier). In the dark systems flumioxazin and metabolites THPA, APF, U@5.5 (uncharacterised), U@23.8 (uncharacterised) were found above 10% AR in the water phase and flumioxazin and metabolite THPA were found to be greater than 10% AR in the sediment phase. Flumioxazin exhibited moderate persistence in the dark aerobic water sediment experiments. Main finding of the irradiated water sediment experiment was the formation of the major photolysis metabolites 482-HA, 482-PHO and PHO-HA in the water phase. An additional major metabolite was found in the water phase for the anaerobic water sediment system (SAT-482-HA-2). FOCUS PEC SW/Sed up to Step 3 were calculated for flumioxazin and up to Step 2 for the metabolites 482-HA, THPA (Δ1-TPA), APF, SAT-482-HA-2, 482-PHO, PHO-HA (FOCUS, 2001). Worst-case PEC SW for uncharacterised metabolites U@5.5 and U@23.8 were calculated as a proportion of the maximum PEC SW of the parent flumioxazin.

The potential for groundwater contamination was assessed by calculation of the 20 years 80th percentile concentration at 1 m depth for flumioxazin and its soil metabolites THPA and Δ1-TPA with the FOCUS GW II scheme (EFSA, 2007; FOCUS, 2009)\(^7\) using the available information as input parameters(worst-case 24 h Koc was used for the parent compound). Leaching resulting from the representative uses in potatoes and tomatoes was simulated with FOCUS models PEARL 4.4.4 and PELMO 4.4.3 for the available scenarios following the representative GAP for winter cereals and sunflowers. Limit of 0.1 µg/L was not exceeded by flumioxazin and its metabolites for any of the uses and scenarios simulated. However, results should be considered to be uncertain until additional reliable adsorption input parameters for parent flumioxazin are available and assessed.

5. Ecotoxicology

The following documents were followed for the risk assessments (European Commission, 2002a,b; SETAC, 2001; EFSA, 2009).

On the basis of the available data and assessments, a low risk to birds and mammals was concluded for the representative uses. However, as discussed in Section 2, available data are not sufficient to rule out an endocrine-mediated mode of action of flumioxazin. Therefore, a data gap and an issue not finalised were identified (see Sections 7 and 9).

\(^7\) A Q_{90} of 2.58 (EFSA, 2007) and Walker equation coefficient of 0.7 was used in these simulations and for the normalisation of the degradation input parameters used in the modelling.
Toxicity data were available for fish, aquatic invertebrates (including sediment dweller organisms), algae and *lemna* for flumioxazin; and on algae and *lemna* for some of the aquatic metabolites. On the basis of these data, flumioxazin was classified as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410. The first-tier risk assessment that considered FOCUS Step 1 exposure estimations resulted in a low risk to fish, sediment dweller organisms and low acute risk to daphnids. However, the chronic study on daphnids was not considered reliable to be used in a low-tier risk assessment for flumioxazin. Therefore, a data gap was identified for an appropriate chronic risk assessment for daphnids. Apart from the issue on the daphnids, it was concluded that algae and aquatic plants are more sensitive to flumioxazin than the other aquatic organisms. Since many of the studies on algae and aquatic plants were not considered as fully reliable, the data set and the pertinent risk assessments for algae and aquatic plants were discussed at the Pesticides Peer Review experts’ meeting 111. The meeting concluded that those end points where the test concentrations were not maintained in the study are likely to underestimate the toxicity. However, it was agreed to not ignore the risk assessments that used those end points, as those risk assessments indicated a high risk to algae and aquatic plants (with FOCUS step 3 exposure estimations). A higher tier outdoor microcosm study on phytoplankton and macrophytes was also available. Using the end points from this study, a low risk to algae and aquatic plants was concluded. This conclusion was agreed by the experts at the meeting.

The risk of the identified aquatic metabolites was assessed as low on the basis of quantitative or qualitative risk assessments. Although it was noted that the available end points for the metabolites APF and 482-PHO are likely to underestimate the toxicity, a low risk was concluded on the basis of the apparent margin of safety reviled by the qualitative risk assessments. A high risk was identified for the uncharacterised metabolites U@5.5 and U@23.8 on the basis of worst-case risk assessments. Therefore, a data gap was identified to address the risk to aquatic organisms of these uncharacterised metabolites.

Using the available laboratory studies, the risk to honeybees and non-target arthropods was assessed as low for the representative uses.

Laboratory studies on earthworms and on soil microorganisms were available for flumioxazin and an earthworm study was available on the soil metabolite Δ¹-TPA. Based on the results of these studies, the risk to non-target soil macro- and microorganisms was assessed as low for the representative uses of flumioxazin. The risk to the soil metabolite THPA was considered to be covered by the risk assessment for the metabolite Δ¹-TPA as it was considered that THPA was present in the earthworm study on metabolite Δ¹-TPA (THPA and Δ¹-TPA are assumed to be in equilibrium in environmental matrices, see Section 4). Moreover, THPA has a similar chemical structure to Δ¹-TPA and the risk assessment on Δ¹-TPA resulted in a large margin of safety.

The pertinent data and risk assessments that were available for non-target terrestrial plants were discussed at the Pesticides Peer Review experts’ meeting 111. On the basis of the available assessments, a low risk was concluded to non-target terrestrial plants provided that risk mitigation that corresponds to a 5-metre no-spray buffer zone is used.

The risk to organisms involved in biological methods for sewage treatment was considered as low for the representative uses of flumioxazin.

### 6. Endocrine disruption properties

An assessment of the endocrine-disrupting properties of flumioxazin in line with ECHA/EFSA Guidance was available and outstanding issues were discussed at Pesticides Peer Review Experts’ Meeting 05 (Joint Mammalian toxicology – ecotoxicology meeting) in June 2020.

With regard to the assessment of the endocrine disruption (ED) potential of flumioxazin for humans according to the ECHA/EFSA guidance (2018), based on the available evidence from standard studies, the T-modality is considered sufficiently investigated and no adversity has been observed for humans. Therefore, the substance does not meet the ED criteria for the T-modality for humans. Regarding oestrogen, androgen and steroidogenesis (EAS) modalities, no EAS-mediated adversity is observed. However, EAS-mediated parameters are not sufficiently investigated (i.e. lack of OECD TG 416, version from 2001 or OECD TG 443) ruling out the possibility to exclude other potential EAS-mediated adverse effects. Regarding EAS-related endocrine activity, only the E-modality is sufficiently investigated and negative. Therefore, further data need to be generated before a conclusion on whether the ED criteria are met for the AS modalities can be drawn.

The conclusions for humans also apply to wild mammals as non-target organisms.
Regarding **non-target organisms other than wild mammals**, the available evidence is not considered sufficient to conclude either on EATS-mediated endocrine activity or on EATS-mediated adversity.

In line with the ‘Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009’, a tiered assessment strategy is recommended. In the case of flumioxazin, where no EATS-mediated adverse effects were observed based on an incomplete data set, level 2 and level 3 test must be required to complete the current data package:

- OECD TG 458 (AR STTA assays)
- OECD TG 456 (H295R Steroidogenesis Assay)
- OPPTS 890.1200 (Aromatase assay)
- A study in line with OECD TG 441 (Hershberger Assay) in case OECD TG 456 and OECD TG 458 and OPPTS 890.1200 are negative
- A study in line with the OECD TG 231 (AMA)8
- A study in line with the OECD TG 229 (FSTRA)

Those tests are relevant to investigate potential EATS-mediated endocrine activity and, if negative, to exclude that flumioxazin has endocrine properties, according to the scientific criteria for the determination of endocrine-disrupting properties as set out in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Regulation (EU) No 2018/605. However, in case of positive result/s based on these tests for at least one modality, additional testing (Level 4/5) might be needed in order to further investigate the adversity (see EFSA, 2020b). In addition to the testing strategy highlighted above, a literature review should be conducted in line with the recommendations of the ECHA/EFSA Guidance on ED.

Due to the above-mentioned lack of data, the ED assessment remains as an issue that could not be finalised. A conclusion on whether the criteria for endocrine disruption for both humans and non-target organisms as set in point 3.6.5 and point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be reached.

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8 Considering that no T-mediated adversity was observed in mammals based on a complete data set, a Xenopus Eleutherobryonic Thyroid Assay (XETA) according to OECD TG 248, instead of the AMA, in the specific case of flumioxazin, could be a suitable alternative as level 3 test to investigate the endocrine activity in amphibians.
7. **Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)**

**Table 1:** Soil

| Compound (name and/or code) | Persistence | Ecotoxicology |
|----------------------------|-------------|---------------|
| flumioxazin                | Moderate (DT$_{50}$ $20^\circ$C = 11.8 d - 34.7 days) | The risk to soil organisms was assessed as low |
| THPA (major photolysis metabolite) (diacid form) | Very low to low (DT$_{50}$ $20^\circ$C = 0.6 days - 4 days) | The risk to soil organisms was assessed as low |
| $\Delta^1$-TPA (major photolysis metabolite) (anhydride form) | Assumed to be in equilibrium with THPA (cyclic anhydride) | The risk to soil organisms was assessed as low |

**Table 2:** Groundwater

| Compound (name and/or code) | Mobility in soil | $> 0.1 \mu g/L$ at 1 m depth for the representative uses$^{(a)}$ | Pesticidal activity | Toxicological relevance | Ecotoxicological activity |
|----------------------------|------------------|-------------------------------------------------|--------------------|------------------------|--------------------------|
| flumioxazin                | Low mobility according available data. A data gap has been identified for a complete and reliable soil adsorption data set | FOCUS: not expected to exceed 0.1 $\mu g/L$ with available information. However, a data gap is identified for a complete and reliable soil adsorption data set | Yes | Yes | Yes |
| THPA                      | Medium to very high ($K_{Foc} = 13 - 339$ mL/kg) | FOCUS: not expected to exceed 0.1 $\mu g/L$ with available information. However, a data gap is identified for reliable soil adsorption data of the parent compound. Confirmation of modelling needed when adsorption data for the parent become available | Not applicable | Assessment not triggered. No studies available | Not applicable |
| $\Delta^1$-TPA             | Assumed to be in equilibrium with THPA (cyclic anhydride). Estimated to be highly mobile in soil with HPLC method | FOCUS: not expected to exceed 0.1 $\mu g/L$ with available information. However, a data gap is identified for reliable soil adsorption data of the parent compound. Confirmation of modelling needed when adsorption data for the parent become available | Not applicable | Assessment not triggered. No studies available | Not applicable |

$^{(a)}$: FOCUS scenarios or relevant lysimeter.
Table 3:  Surface water and sediment

| Compound (name and/or code)                                                                 | Ecotoxicology                                                                 |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Flumioxazin (surface water and sediment)                                                   | Data gap                                                                     |
| 482-HA (surface water and sediment)                                                         | The risk to aquatic organisms was assessed as low                            |
| THPA (surface water and sediment)                                                           | The risk to aquatic organisms was assessed as low                            |
| Δ¹-TPA (surface water)                                                                     | The risk to aquatic organisms was assessed as low                            |
| APF (surface water)                                                                        | The risk to aquatic organisms was assessed as low                            |
| 482-PHO (surface water)                                                                    | The risk to aquatic organisms was assessed as low                            |
| PHO-HA (surface water)                                                                      | The risk to aquatic organisms was assessed as low                            |
| SAT-482-HA-2 (surface water, anaerobic water/sediment conditions)                          | The risk to aquatic organisms was assessed as low                            |
| U@23.8 (surface water)                                                                      | Data gap                                                                     |
| U@5.5 (surface water)                                                                       | Data gap                                                                     |

Table 4:  Air

| Compound (name and/or code) | Toxicology                                                                 |
|-----------------------------|---------------------------------------------------------------------------|
| flumioxazin                 | Not acutely toxic by inhalation to rats (LC₅₀ > 3.93 mg/L)                |
8. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

- Method of analysis for 482-HA in surface water (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- ILV for the QuEChERS method acidic matrix (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 1).
- Sufficient information to address whether the batches used in the toxicological studies cover the technical specification including the purity and impurity profile of toxicological studies (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Sufficient information to address the toxicological relevance of impurities in the technical specification (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 2).
- Sufficient residue trial data in sunflower in SEU (relevant for the representative use in sunflower in SEU; submission date proposed by the applicant: unknown; see Section 3).
- An assessment of the potential for uptake of residues (including soil metabolites) in rotational crops (relevant for all representative uses; submission date proposed by the applicant: unknown; see Section 3).
- Additional soil adsorption study needs to be provided for flumioxazin to complete the data set and overcome the limitations of the available study (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 4).
- An appropriate chronic risk assessments for daphnids (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- The risk assessment to aquatic organisms of the uncharacterised metabolites U@5.5 and U@23.8 need to be further addressed (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 5).
- Tests according to OECD TG 458, OECD TG 456 and OPPTS 890.1200 would be needed for further investigating the endocrine disruption potential of flumioxazin. Assuming that the three level 2 tests (OECD TG 458, OECD TG 456, OPPTS 890.1200) will be performed in parallel, the applicant should complete the data package to support a conclusion on the absence of EATS-mediated adversity/endocrine activity, as explained in Section 3.4.1 of the Guidance, within an estimated time period of 9 months. However, if all these level 2 assays are negative, further test according to OECD TG 441 is needed and an additional estimated time period of 20 months would be required. Moreover, if any level 2/3 assays is positive, further test according to OECD TG 443 or OECD TG 416 is needed in order to further investigate the adversity and an additional estimated time period of 24 months would be required (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 6 of the present conclusion and EFSA, 2020b for further information).
- A level 3 study according to OECD TG 229 (FSTRA, fish short-term reproduction assay) and a level 3 study according to OECD TG 231 (AMA, Amphibian Metamorphosis Assay) are required to address the ED properties. Considering that no T-mediated adversity was observed in mammals based on a complete data set, a Xenopus Eleutheroembryonic Thyroid Assay (XETA) according to OECD TG 248, instead of the AMA, in the specific case of flumioxazin, could be a suitable alternative as level 3 test to investigate the endocrine activity. In case of positive findings, further data (i.e. level 4/5 studies) might be needed in order to further investigate the adversity to reach a conclusion on the ED criteria for non-target organisms. Following the testing strategy according to the ECHA/EFSA guidance, a minimum of 19 months would be necessary to conduct the level 3/4 studies as indicated above in order to draw a conclusion on the ED criteria for non-target organisms. If there is a positive evidence from the results of those studies, further testing may be necessary, and therefore, the previous time period would be extended up to a further 28 months (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 6 of the present conclusion and EFSA, 2020b for further information).
• A literature review according to the recommendations of the ECHA/EFSA Guidance should be conducted and should be submitted together with the additional studies highlighted in data gaps above to address ED properties (relevant for all representative uses evaluated; submission date proposed by the applicant: unknown; see Section 6 of the present conclusion and EFSA, 2020b for further information).

9. **Particular conditions proposed to be taken into account to manage the risk(s) identified**

A low risk could only be concluded to non-target terrestrial plants when a risk mitigation measure with comparable efficiency to the efficiency of a 5-metre no-spray buffer zone was considered. Therefore, risk mitigation measure with comparable efficiency to the efficiency of a 5-metre no-spray buffer zone is proposed in order to mitigate the risk to non-target terrestrial plants (see Section 5).

10. **Concerns**

10.1. **Issues that could not be finalised**

An issue is listed as ‘could not be finalised’ if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011 and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as ‘could not be finalised’ if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) The assessment of the endocrine-disrupting properties of flumioxazin for humans and non-target organisms could not be finalised due to the incomplete data sets (see Section 6 of this conclusion and EFSA 2020b for further information).

2) Available ground water exposure assessment should be considered uncertain until additional reliable adsorption input parameters for parent flumioxazin became available.

10.2. **Critical areas of concern**

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

3) Insufficient information was available to compare whether the technical material specification proposed was comparable to the material used in the testing that was used to derive the toxicological reference values.

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9 Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.
10.3. Overview of the concerns identified for each representative use considered (Table 5)

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

In addition to the issues indicated in Table 5 below, the technical material specification proposed was not comparable to the material used in the testing that was used to derive the toxicological reference values.

Table 5: Overview of concerns

| Representative use                              | Winter wheat | Sunflower pre-emergence | Sunflower post-emergence |
|------------------------------------------------|--------------|-------------------------|--------------------------|
| Operator risk                                  | Risk identified |                         |                          |
| Worker risk                                    | Risk identified |                         |                          |
| Resident/bystander risk                        | Risk identified |                         |                          |
| Consumer risk                                  | Risk identified |                         |                          |
| Risk to wild non-target terrestrial vertebrates | Risk identified |                         |                          |
| Risk to wild non-target terrestrial organisms other than vertebrates | Risk identified |                         |                          |
| Risk to aquatic organisms                      | Risk identified |                         |                          |
| Groundwater exposure to active substance        | Assessment not finalised |              |                          |
| Groundwater exposure to metabolites            | Legal parametric value breached(a) |              | X X X                    |
|                                                | Parametric value of 10 μg/L(b) breached |              |                          |
|                                                | Assessment not finalised |              |                          |

The superscript numbers relate to the numbered points indicated in Sections 10.1 and 10.2. Where there is no superscript number, see Sections 2–7 for further information.

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission (2003).

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Abbreviations

| Symbol | Description |
|-------|-------------|
| 1/n   | slope of Freundlich isotherm |
| λ     | wavelength |
| λ     | wavelength |
| ε     | decadic molar extinction coefficient |
| ADE   | actual dermal exposure |
| ADI   | acceptable daily intake |
| ACronym | Definition |
|---------|------------|
| AF      | assessment factor |
| AOEL    | acceptable operator exposure level |
| AP      | alkaline phosphatase |
| AR      | applied radioactivity |
| AR      | androgen receptor |
| ARfD    | acute reference dose |
| AV      | avoidance factor |
| BUN     | blood urea nitrogen |
| bw      | body weight |
| CAS     | Chemical Abstracts Service |
| CHO     | Chinese hamster ovary cells |
| CI      | confidence interval |
| CL      | confidence limits |
| DAR     | draft assessment report |
| DAT     | days after treatment |
| DM      | dry matter |
| DT₅₀    | period required for 50% dissipation (define method of estimation) |
| ECHA    | European Chemicals Agency |
| EEC     | European Economic Community |
| FAO     | Food and Agriculture Organization of the United Nations |
| FOCUS   | Forum for the Co-ordination of Pesticide Fate Models and their Use |
| GAP     | Good Agricultural Practice |
| HPLC    | high-pressure liquid chromatography or high-performance liquid chromatography |
| HPLC-MS | high-pressure liquid chromatography–mass spectrometry |
| ILV     | independent laboratory validation |
| ISO     | International Organization for Standardization |
| IUPAC   | International Union of Pure and Applied Chemistry |
| iv      | intravenous |
| 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) |
| K_foc   | Freundlich organic carbon adsorption coefficient |
| LC      | liquid chromatography |
| LC₅₀    | lethal concentration, median |
| LC-MS   | liquid chromatography–mass spectrometry |
| LC-MS-MS| liquid chromatography with tandem mass spectrometry |
| LOAEL   | lowest observable adverse effect level |
| mm      | millimetre (also used for mean measured concentrations) |
| MOA     | mode of action |
| MRL     | maximum residue level |
| MS      | mass spectrometry |
| NOAEL   | no observed adverse effect level |
| OECD    | Organisation for Economic Co-operation and Development |
| OM      | organic matter content |
| PEC     | predicted environmental concentration |
| PEC_soil| predicted environmental concentration in soil |
| PPE     | personal protective equipment |
| QuEChERS| Quick, Easy, Cheap, Effective, Rugged, and Safe (analytical method) |
| RAC     | Committee for Risk Assessment |
| RAR     | Renewal Assessment Report |
| SMILES  | simplified molecular-input line-entry system |
| TK      | technical concentrate |
| WHO     | World Health Organization |
Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2020.6246
## Appendix B – Used compound codes

| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation | Structural formula<sup>(b)</sup> |
|---------------------------------|-----------------------------|---------------------------------|
| **flumioxazin**                | \(N-(7\text{-fluoro}-3,4\text{-dihydro}-3\text{-oxo}-4\text{-prop-2-ynyl}-2\text{H}-1,4\text{-benzoxazin-6-yl})\text{cyclohex-1-ene-1,2-dicarboximide} \) \( O=C4C=1CCCCC=1C(=O)NH4c2cc3c(cc2F)OCC(=O)N3CC#C \) | ![flumioxazin](image) |
| **THPA**                       | cyclohex-1-ene-1,2-dicarboxylic acid \( OC(=O)C=1CCCCC=1C(=O)O \) | ![THPA](image) |
| **THPA-2Na**                   | disodium cyclohex-1-ene-1,2-dicarboxylate \([\text{Na}^+],[\text{Na}^+].O=C([O=])C=1CCCCC=1C([O=])=O\) | ![THPA-2Na](image) |
| **\(\Delta\text{1-TPA}\)**    | 4,5,6,7-tetrahydro-2-benzofuran-1,3-dione \( O=C1OC(=O)C=2CCCCC1=2 \) | ![\(\Delta\text{1-TPA}\)](image) |
| **482-HA**                     | 2-\(\{7\text{-fluoro}-3\text{-oxo}-4\text{-prop-2-ynyl-1-yl}\}-3,4\text{-dihydro-2H-1,4-benzoxazin-6-yl}\)carbamoyl cyclohex-1-ene-1-carboxylic acid \( O=C(=O)C=1CCCCC=1C(=O)Nc2cc3c(cc2F)OCC(=O)N3CC#C \) | ![482-HA](image) |
| **APF**                        | 6-amino-7-fluoro-4-(prop-2-ynyl-1-yl)-2\text{H}-1,4-benzoxazin-3(4\text{H})-one \( Nc1cc2c(cc1F)OCC(=O)N2CC#C \) | ![APF](image) |
| **482-PHO**                    | \(N-(2\text{-propynyl})-4\{4\text{-carboxy-3-fluoro-2-(3,4,5,6-tetrahydrophthalimido)-2-butenyldiene}\}azetidine-2\text{-one} \( O=C(=O)CC(\{F\})=C(=C\text{-C1/CC(=O)N1CC#C})N3C(=O)C=2CCCCC\text{-2C3}=O \) | ![482-PHO](image) |
| Code/trivial name<sup>(a)</sup> | IUPAC name/SMILES notation | Structural formula<sup>(b)</sup> |
|-------------------------------|----------------------------|---------------------------------|
| **PHO-HA**                    | \(N\text{-}(2\text{-propynyl})\text{-}4\text{-}[4\text{-carboxy-3-fluoro-2-(2-carboxy-1-cyclohexencarbonylamino)-2-butenylidene}]\text{azetidine}\text{-}2\text{-one} \)  
\[\text{O} = \text{C}2\text{C} \{=\text{C} \text{C} \{(\text{NC} \text{=O}) \text{C} = \text{1CCC} \text{C} = \text{1C} \text{=O} \text{O} \text{=C} \text{F}\text{C} \text{C} \text{=O} \text{O}\} \text{N}2\text{CC} \text{#C}\] | ![Structural formula](image1) |
| **SAT-482-HA-2**              | \((1\text{S},2\text{S})\text{-}2\text{-}[7\text{-fluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl}]\text{carbamoyl} \text{cyclohexanecarboxylic acid} \)  
\[\text{O} = \text{C} \text{(O)} \text{[C@H]} \text{3CCC[C@H]} \text{3C} \text{=O} \text{Nc1cc2c(c}(\text{C} \text{F})\text{OCC(=O)N2CC#C}) \] | ![Structural formula](image2) |
| **U@23.8**                   | Not characterised           |                                  |
| **U@5.5**                    | Not characterised           |                                  |

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

<sup>(b)</sup> ACD/ChemSketch 2018.2.2 ACD/Labs 2018 Release (File version C60H41, Build 106041, 7 December 2018).