CONCLUSION ON PESTICIDES PEER REVIEW

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Peer review of the pesticide risk assessment for the active substance flumioxazin in light of negligible exposure data submitted

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessment carried out by the competent authority of the rapporteur Member State, Czech Republic, for the pesticide active substance flumioxazin are reported. The European Commission requested EFSA to conduct a peer review and provide its conclusions on whether exposure of humans to flumioxazin can be considered negligible, taking into account the European Commission's draft guidance on this topic. 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 reliable endpoints, derived from the studies and the literature data presented in the dossier and considered appropriate for use in regulatory risk assessment, are presented.

Keywords: flumioxazin, peer review, negligible exposure, risk assessment, pesticide, herbicide

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Summary

Flumioxazin is listed in Annex I of Commission Regulation (EU) No 1141/2010 as amended by Commission Implementing Regulation (EU) No 380/2013. In accordance with Article 16 of the Regulation, the European Food Safety Authority (EFSA) finalised a conclusion on the peer review of the pesticide risk assessment of the active substance on 4 June 2014 and provided its conclusion to the European Commission.

Flumioxazin has harmonised classification and labelling as toxic for reproduction category 1B and a critical area of concern was identified in the previous EFSA conclusion with regard to the approval criteria, Annex II, Point 3.6.4 of Regulation (EC) No 1107/2009. As part of the preceding peer review for renewal of approval of flumioxazin, toxic effects were observed in endocrine organs and therefore the second interim provision of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 indicates that flumioxazin may be considered to have endocrine-disrupting properties. Given the harmonised classification and labelling and the potential impact on the renewal of the approval, the European Commission invited the applicant Sumitomo Chemical Agro Europe S.A.S. to provide further information to demonstrate that the exposure of humans to flumioxazin is negligible under realistic conditions of use.

The applicant, Sumitomo Chemical Agro Europe S.A.S. submitted an updated dossier in January 2016. The European Commission then requested the rapporteur Member State (RMS), Czech Republic, to carry out an evaluation of this information and to submit its assessment in the format of a revised renewal assessment report (RAR). The RMS provided the revised RAR on 17 October 2017 to EFSA; EFSA distributed the revised RAR to all Member States for comments on 18 October 2017, and provided comments as well. EFSA collated all comments received and provided its scientific view on these comments. However, based on the comments received, it became apparent that a new revision of the assessment was needed in order to allow for a comprehensive assessment to be conducted. The RMS provided the revised RAR on 8 March 2018 to EFSA. EFSA distributed the revised assessment to all Member States for comments on 12 March 2018, and provided comments as well.

Considering the representative uses on winter **wheat and sunflower** the dietary exposure (short-term and long-term) was below 1% of the acute reference dose (ARfD) and acceptable daily intake (ADI), respectively, for all consumer groups. Residues according to the residue definition for risk assessment as determined in residue trials were below the lowest validated limit of quantification (LOQ) for wheat of 0.01 mg/kg and for sunflower of 0.05 mg/kg. If the currently established maximum residue levels (MRLs) are used, the theoretical maximum daily intake (TMDI) corresponds to 1.2% of the ADI (WHO cluster diet B) and highest acute exposure to 1% of the ARfD (wheat, UK 4–6 years old child).

Considering the representative uses on **wheat** the non-dietary exposure (short-to long-term) for operators were up to 3.46% of the acceptable operator exposure level (AOEL) with the use of soluble bags and risk mitigation measures. Under this situation the margin of exposure is 3,936 for the reproductive effect. The estimates for acute exposure were up to 17.05% of the acute acceptable operator exposure level (AAOEL) with the use of soluble bags and risk mitigation measures. Considering this scenario the margin of exposure is 586 for the reproductive effect. The exposure estimates for workers were up to 1.36% of the AOEL with the use of workwear, and a margin of exposure of 10,000. The exposure estimates for residents and bystanders were up to 6.59% of the AOEL and 3.67% of the AAOEL, taking into account a buffer zone of 10 m and drift reduction nozzles. Under this situation the margin of exposure was 2,069 and 2,804 for short- to long-term exposure and acute exposure, respectively.

Considering the representative uses on **sunflower** the non-dietary exposure (short- to long-term) for operators were up to 4.79% of the AOEL with the use of soluble bags and risk mitigation measures. Under this situation, the margin of exposure is 2,848 for the reproductive effect. The estimates for acute exposure were up to 23.64% of the AAOEL with the use of soluble bags and risk mitigation measures. Considering this situation, the margin of exposure is 423 for the reproductive effects. The exposure estimates for workers were up to 2.73% of the AOEL with the use of workwear, resulting in a margin of exposure of 5,000. The estimates for residents and bystanders were up to 7.73% of the AOEL and 3.67% of the AAOEL taking into account a buffer zone of 10 m and drift reduction nozzles. Under this situation, the margin of exposure was 1,765 and 2,727 for short- to long-term exposure and acute exposure respectively.

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Background

Flumioxazin is listed in Annex I of Commission Regulation (EU) No 1141/2010[1] as amended by Commission Implementing Regulation (EU) No 380/2013[2]. In accordance with Article 16 of the Regulation, the European Food Safety Authority (EFSA) finalised a conclusion on the peer review of the pesticide risk assessment of the active substance on 4 June 2014 (EFSA, 2014a) and provided its conclusion to the European Commission.

Annex II of Regulation (EU) No 1107/2009[3] provides in its points 3.6.3, 3.6.4 and 3.6.5 that active substances classified on the basis of Regulation (EC) No 1272/2008[4] as carcinogen category 1A or 1B or toxic for reproduction category 1A or 1B, or having endocrine-disrupting properties which may cause adverse effects on humans cannot be approved unless the exposure of humans to that active substance in a plant protection product under realistic proposed conditions of use, is negligible. These conditions under which negligible exposure is assumed is precondition for approval of substances in accordance with Article 4 of the Regulation (EU) No 1107/2009 read in combination with these points. The European Commission shall propose a decision on renewal/non-renewal of approval for active substances considered under Regulation (EU) No 1107/2009 taking into account the approval criteria of Annex II, points 3.6.3, 3.6.4 and 3.6.5 of that Regulation.

Flumioxazin has a harmonised classification and labelling as toxic for reproduction category 1B in accordance with the provisions of Regulation (EC) No 1272/2008 and a critical area of concern was identified with regard to the approval criteria, Annex II, Point 3.6.4 of Regulation (EC) No 1107/2009. Toxic effects were observed in endocrine organs and therefore, the second interim provision of Annex II, Point 3.6.5 of Regulation (EC) No 1107/2009 indicates that flumioxazin may be considered to have endocrine-disrupting properties. Annex II, Point 3.6.4 and Point 3.6.5 of Regulation 1107/2009 state respectively that a substance which is classified as toxic for reproduction category 1A or 1B or those that are considered to have endocrine-disrupting properties should not be approved 'unless the exposure of humans to that active substance in a plant protection product, under realistic proposed. Given the harmonised classification and labelling and the potential impact on renewal of approval, the European Commission invited the applicant Sumitomo Chemical Agro Europe S.A.S. to provide further information to demonstrate that the exposure of humans to flumioxazin, under realistic conditions of use, is negligible. The European Commission then requested the rapporteur Member State (RMS), Czech Republic, to carry out an evaluation of this information and to submit its assessment in the format of a revised RAR to EFSA.

By means of a general mandate received on 13 January 2016, the European Commission requested EFSA to conduct a peer review and provide its conclusions on particular active substances, to be communicated on an ad hoc basis, on whether exposure of humans to an active substance, under realistic conditions of use, can be considered negligible, taking into account the draft 'Technical guidance on points 3.6.3 to 3.6.5 of Annex II to Regulation (EC) No 1107/2009, in particular regarding the demonstration of negligible exposure to an active substance in a plant protection product under realistic conditions of use'. With a clarification to the general mandate received on 17 May 2016, the European Commission clarified that taking into account the absence of a final guidance document and on-going discussions in the Standing Committee on Plants, Animals, Food and Feed (PAFF Committee), the draft guidance document made available for stakeholder consultation and published on Commissions' website on 25 June 2015 should be considered (draft dated May 2015; SANCO/2014/12096 (European Commission, 2015)). In the absence of agreed threshold values for assessing negligible exposure, a conclusion regarding such agreed threshold is not possible. However, in order to provide risk managers with the relevant information for decision making, EFSA was requested to (a) calculate the actual expected exposure values in absolute values and percentage of the established toxicological reference values (e.g. acceptable operator exposure level (AOEL)); (b) consider potential technical mitigation

[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 322, 8.12.2011, p. 10–19.

[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 116, 26.4.2013, p. 4.

[3] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council 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.

[4] 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.

measures to reduce exposure as those mentioned in the draft guidance, that have been proposed by the applicant and/or by the RMS, or by EFSA, if and when appropriate.

The applicant, Sumitomo Chemical Agro Europe S.A.S. submitted an updated dossier in January 2016. The European Commission then requested the RMS, Czech Republic, to carry out an evaluation of this information and to submit its assessment in the format of a revised renewal assessment report (RAR). The RMS provided the revised RAR on 17 October 2017 to EFSA (Czech Republic, 2017); EFSA distributed the revised RAR to all Member States for comments on 18 October 2017, and provided comments as well. EFSA collated all comments received and provided its scientific view on these comments. However, based on the comments received, it became apparent that a new revision of the assessment was needed in order to allow for a comprehensive assessment to be conducted. The RMS provided the revised RAR on 8 March 2018 to EFSA. EFSA distributed the revised assessment to all Member States for comments on 12 March 2018, and provided comments as well.

The revised RAR and the compiled commenting tables were discussed at Pesticides Peer Review Experts' teleconference in the area of mammalian toxicology in April 2018. Details of the issues discussed, together with the outcome of these discussions were recorded in the meeting report.

A final consultation on the conclusions arising from the peer review took place with Member States via a written procedure in August 2018.

The conclusions laid down in this report were reached on the basis of the peer review of the RMS's evaluation of the negligible exposure data submitted. 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 compilation of comments to the conclusion. The peer review report (EFSA, 2018) 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 revised RAR;
- the report of the scientific consultation with Member State experts;
- the comments received on the draft EFSA conclusion.

Given the importance of the revised RAR (Czech Republic, 2018) and the peer review report, 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 European Union (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-2*H*-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 Appendix A.

Conclusions of the evaluation

The applicant has submitted to the Commission information to demonstrate that the exposure of humans to flumioxazin can be considered negligible under the proposed condition of use.

The assessment of the information was presented in a revised RAR (Czech Republic, 2018) prepared according to the draft Technical Guidance Document on assessment of negligible exposure of an active substance in a plant protection product under realistic conditions of use (points 3.6.3 to 3.6.5, and 3.8.2 of Annex II of Regulation (EC) No 1107/2009) SANCO/2014/12096 (European Commission, 2015).

1. Negligible exposure to humans

The following guidance documents were followed in the production of this conclusion: SANCO/2014/12096 (European Commission, 2015) and EFSA Guidance on the assessment of exposure of operators, workers, residents and bystanders (EFSA, 2014b).

1.1. Dietary exposure

In the available primary crop metabolism studies, the identification of any discrete residue other than parent flumioxazin did not succeed (sugar cane, grapevines, soya bean), was indicative (peanut) or was not attempted because of total residues < 0.01 mg/kg (grapes, apple). Radiochromatograms of peanut hull samples suggested the presence of the metabolites tetrahydrophthalic acid (THPA) and 1-OH-HPA-1. Flumioxazin was recovered only upon foliar treatment in the study in sugar cane (68–88% total radioactive residue (TRR)) while it was not identified as a residue in the soil-applied studies.

Comparison of chromatographic profiles led to the conclusion that the picture observed in crops after soil treatment is different compared to foliar-treated crops, suggesting that the residue pattern in crops after soil application might be driven by the uptake of soil metabolites. Moreover, in some of the experiments residues associated with the THP-compartment of the molecule appeared to be taken up preferentially, indicating the preceding breakdown of the imide linkage in the parent molecule. Consistent with this observation, it was concluded previously that flumioxazin exhibited moderate persistence in soil (20°C laboratory DT_{90} up to 115 days) and it degraded into a number of metabolites, of which THPA and its corresponding cyclic anhydride were major transformation products, predominantly formed by photolysis that exhibited very low to low soil persistence (20°C laboratory DT_{90} up to 13 days) (EFSA, 2014a). Separate investigations on the nature and level of residues in rotational crops were concluded as being unnecessary for the uses being assessed, as applications are pre or early post emergence (when not more than 4 leaves have emerged), so the interval to when following crops will be planted (following harvest at maturity and subsequent cultivation) would be expected to be longer than 115 days.

Based on the plant metabolism data from post- and pre-emergence application and based on expert judgment, the residue definition for monitoring and risk assessment in all commodities of plant origin (EFSA, 2014a) has been set as flumioxazin. New data, that would have required reconsideration of the previous expert decision (EFSA, 2014c), were not made available under the current submission for the assessment of negligible exposure. The available metabolism studies are sufficient to support the uses under assessment, i.e. pre-emergence and early post-emergence application in sunflower and winter wheat.

Seven (7) residue trials in northern Europe (NEU) in wheat with foliar application during beginning stem elongation are available. The residues of flumioxazin were consistently below 0.01 mg/kg (limit of quantification (LOQ)) in mature grain and straw. Two trials each in NEU and southern Europe (SEU) in sunflowers with early post-emergence application did not show result in residues of flumioxazin above 0.05 mg/kg (LOQ) in sunflower seed. The applied analytical methods were sufficiently validated and integrity of residues during sample storage was demonstrated for flumioxazin. As residues < LOQ in commodities at harvest could be reasonably expected from the metabolism studies and were confirmed by the available trials, a reduced number of residue trials is acceptable.

The consumer dietary risk assessment was conducted with EFSA Pesticide Residues Intake Model (PRIMo) rev.2, assuming residues in wheat grain and sunflower seed at the respective LOQ in the residue trials. The estimated chronic and acute dietary exposure was below 1% of the acceptable daily intake (ADI) and acute reference dose (ARfD), respectively, for all consumer groups. If the currently established maximum residue levels (MRLs) are used (wheat 0.02* mg/kg; sunflower seed 0.05* mg/kg), the theoretical maximum daily intake (TMDI) corresponds to 1.2% ADI (WHO cluster diet B) and highest acute exposure to 1% ARfD (wheat, UK 4- to 6-year-old child).

1.2. Non-dietary exposure

The reference values for flumioxazin agreed during the peer review (EFSA, 2014a) are presented in Table 1.

* Indicates lower limit of analytical determination.

Table 1: Reference values for flumioxazin (EFSA, 2014a)

	Value (mg/kg bw (per day))	Study	Uncertainty factor
ADI[(a)]	0.018	Rat, 2-year	100
ARfD[(a)]	0.1	Rat, developmental	100
AOEL[(a)]	0.022	Rat, 90-day	100

bw: body weight.
(a): ADI: acceptable daily intake; ARfD: acute reference dose; AOEL: acceptable operator exposure level (short- to long-term exposure).

In the context of preparation of the 48th session of the Codex Committee on Pesticide Residues (CCPR meeting), EFSA in (EFSA, 2016) reported that Joint Meeting on 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, JMPR) (FAO, 2015) derived a lower developmental no observed adverse effect levels (NOAEL) than the one derived during the EFSA peer review (i.e. 3 mg/kg bw per day instead of 10 mg/kg bw per day from the developmental toxicity study in rats) in (EFSA, 2014a). JMPR described an increased incidence of malformations (cardiac ventricular septal defects) in the foetuses at 10 mg/kg bw per day. EFSA noted that tabular data were missing in the RAR. After having checked the raw data EFSA agreed with JMPR to consider the developmental NOAEL 3 mg/kg bw per day. EFSA agreed to set a lower ARfD of 0.03 mg/kg bw, considering the increased incidence of malformations in foetuses, as proposed by JMPR.

The revision of the ARfD and setting of the acute acceptable operator exposure level (AAOEL) was discussed during the ad hoc pesticides peer review experts' teleconference TC 188 on mammalian toxicology. The experts did not reach consensus. One expert supported the JMPR opinion that the NOAEL should be set at 3 mg/kg. Another expert abstained. The RMS remained of the opinion that the developmental NOAEL is 10 mg/kg bw per day. Regarding the setting of the AAOEL, all experts agreed that it could be based on the same basis as the ARfD. Under the current assessment EFSA revised the setting of the relevant NOAEL for the critical effect in the developmental toxicity study in rats (i.e. 3 mg/kg bw per day) and the setting of the ARfD and AAOEL (i.e. 0.03 mg/kg bw). The calculations reported under the current assessment reflect EFSA's view and not the RMS' view.

The dermal absorption values of flumioxazin in 'Flumioxazin 50 WP' were agreed during the peer review as being 2.8% for the concentrate and of 18.5% for the dilution (*in vivo* rat dermal absorption study). In the context of the negligible exposure application, an *in vitro* human dermal absorption study was submitted. The RMS proposed new dermal absorption values of flumioxazin for 'Flumioxazin 50 WP' of 0.5% for the concentrate and 8% for the dilution. These new values have been used for the calculations reported under the current assessment (Table 2).

Table 2: Reference values for flumioxazin currently supported by EFSA

	Value (mg/kg bw (per day))	Study	Uncertainty factor
ADI[(a)]	0.018	Rat, 2-year	100
ARfD[(a)]	0.03	Rat, developmental	100
AOEL[(a)]	0.022	Rat, 90-day	100
AAOEL[(a)]	0.03	Rat, developmental	100

bw: body weight.
(a): ADI: acceptable daily intake; ARfD: acute reference dose; AOEL: acceptable operator exposure level (short to long term exposure); AAOEL: acute acceptable operator exposure level (acute exposure).

First tier assessment:

Exposure estimates have been provided for operators, workers, bystanders and residents, for the representative uses on wheat and sunflower. The exposure assessment for residents also covers longer term exposure for bystanders. The acute exposure assessment for the bystander also covers acute exposure scenarios for the resident. The results, including possible risk mitigation measures, are presented in Tables 3, 4, 5 and 6 for the representative uses in wheat and in Tables 7, 8, 9 and 10 for representative uses in sunflower.

Second tier assessment:

Considerations were also given to the margin of exposure (MoE) between non-dietary exposure and the NOAELs for the critical effects (i.e. 3 mg/kg bw per day). The results are also included in the Tables 3, 4, 5 and 6 (wheat uses) and Tables 7, 8, 9 and 10 (sunflower uses).

Table 3: Non-dietary exposure scenarios and margin of exposure (MoE) – operators

Operators – use in wheat (30 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL or AAOEL[(a)]**	**MoE[(c)] Repr**
Short to long term exposure	Work wear (arms, body and legs covered)	0.0441	200.45	68
	Work wear + gloves during mixing/loading (M/L)	0.0414	188.18	72
	Work wear + gloves during M/L and application (A)	0.0412	187.27	73
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L[(b)]	0.0105	47.73	286
	Work wear + gloves and RPE (FP1, P1 and similar) during M/L and A[(b)]	0.0105	47.73	286
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L[(b)]	0.0044	20.00	682
	Work wear + gloves and RPE (FP2, P2 and similar) during M/L and A	0.0044	20.00	682
	Work wear + gloves during M/L and A + drift reducing nozzles	0.0411	186.82	73
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles	0.0105	47.73	286
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + drift reducing nozzles	0.0043	19.55	698
	Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0047	21.36	638
	Soluble bags, Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0008	3.46	3936
Acute exposure	Work wear (arms, body and legs covered)	0.0973	324.33	31
	Work wear + gloves during mixing/loading (M/L)	0.0874	291.33	34
	Work wear + gloves during M/L and application (A)	0.0880	293.33	34
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L[(b)]	0.0262	87.33	115
	Work wear + gloves and RPE (FP1, P1 and similar) during M/L and A	0.0261	87.00	115
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L[(b)]	0.0138	46.00	217
	Work wear + gloves and RPE (FP2, P2 and similar) during M/L and A	0.0138	46.00	217
	Work wear + gloves during M/L and A + drift reducing nozzles	0.0833	277.67	36
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles	0.0215	71.67	140
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + drift reducing nozzles	0.0092	30.67	326
	Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0133	44.30	226
	Soluble bags, Work wear + gloves during M/L+ RPE (FP2, P2 and similar) during M/L + closed cabin	0.0051	17.05	586

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure).
(b): PPE: personal protective equipment; RPE: respiratory protective equipment.
(c): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure) or reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.

Table 4: Non-dietary exposure scenarios and margin of exposure (MoE) – workers

Worker – use in wheat (30 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL[(a)]**	**Repr[(a)]**
Short- to long-term exposure	Work wear	0.0003	1.36	10,000

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure); MoE: margin of exposure for carcinogenicity (ratio between critical systemic NOAEL and estimated exposure).

Table 5: Non-dietary exposure scenarios and margin of exposure (MoE) – residents

Resident – use in wheat (30 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL[(a)]**	**MoE[(b)] Repr**
All pathways – child	Buffer zone 2–3 m	0.0016	7.27	1,875
All pathways – adult		0.0005	2.27	6,000
All pathways – child	Buffer zone 10 m	0.0015	6.82	2,000
All pathways – adult		0.0004	1.82	7,500
All pathways – child	Buffer zone 10 m +	1.45E-03	6.59	2,069
All pathways – adult	Drift reduction nozzles 50%	4.20E-04	1.91	7,143

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure); AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure), being the ratio between critical systemic NOAEL and estimated exposure.

Table 6: Non-dietary exposure scenarios and margin of exposure (MoE) – bystanders

Bystander – use in wheat (30 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AAOEL[(a)]**	**MoE[(b)] Repr**
Child:	Buffer zone 2–3 m			
Spray drift		0.0007	2.33	4,286
Vapour		0.0011	3.67	2,727
Surface deposits		0.0002	0.67	15,000
Entry in crops		0.0004	1.33	7,500
Adult:	Buffer zone 2–3 m			
Spray drift		0.0002	0.67	15,000
Vapour		0.0002	0.67	15,000
Surface deposits		0.0000	0.00	60,852
Entry in crops		0.0002	0.67	15,000
Child:	Buffer zone 10 m			
Spray drift		0.0004	1.33	7,500
Vapour		0.0011	3.67	2,727
Surface deposits		0.0000	0.00	79,026
Entry in crops		0.0004	1.33	7,500
Adult:	Buffer zone 10 m			
Spray drift		0.0001	0.33	30,000
Vapour		0.0002	0.67	15,000
Surface deposits		0.0000	0.00	272,232
Entry in crops		0.0002	0.67	15,000
Child:	Buffer zone 10 m+ Drift reduction nozzles 50%			
Spray drift		1.96E-04	0.65	15,306
Vapour		1.07E-03	3.57	2,804
Surface deposits		1.90E-05	0.06	157,895
Entry in crops		4.05E-04	1.35	7,407

Bystander – use in wheat (30 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AAOEL[a]**	**MoE[b] Repr**
Adult: Spray drift Vapour Surface deposits Entry in crops	Buffer zone 10 m + Drift reduction nozzles 50%	3.97E-05	0.13	75,567
		2.30E-04	0.77	13,043
		5.51E-06	0.02	544,465
		2.25E-04	0.75	13,333

bw: body weight.
(a): AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.

Table 7: Non-dietary exposure scenarios and margin of exposure (MoE) – operators

Operators– use in sunflower (50 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL or AAOEL[a]**	**MoE[c] Repr**
Short- to long-term exposure	Work wear (arms, body and legs covered)	0.0524	238.18	57
	Work wear + gloves during mixing/loading (M/L)	0.0484	220.00	62
	Work wear + gloves during M/L and application (A)	0.0480	218.18	63
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L[b]	0.0124	56.36	242
	Work wear + gloves and RPE (FP1, P1 and similar) during M/L and A[b]	0.0124	56.36	242
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L[b]	0.0053	24.09	566
	Work wear + gloves and RPE (FP2, P2 and similar) during M/L and A	0.0052	23.64	577
	Work wear + gloves during M/L and A + drift reducing nozzles	0.0479	217.73	63
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles	0.0123	55.91	244
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + drift reducing nozzles	0.0051	23.18	588
	Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0057	25.91	526
	Soluble bags, Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0011	4.79	2848
Acute exposure	Work wear (arms, body and legs covered)	0.1056	352.00	28
	Work wear + gloves during mixing/loading (M/L)	0.0910	303.33	33
	Work wear + gloves during M/L and application (A)	0.0899	299.67	33
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L[b]	0.0273	91.00	110
	Work wear + gloves and RPE (FP1, P1 and similar) during M/L and A	0.0273	91.00	110
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L[b]	0.0148	49.33	203
	Work wear + gloves and RPE (FP2, P2 and similar) during M/L and A	0.0148	49.33	203
	Work wear + gloves during M/L and A + drift reducing nozzles	0.0850	283.33	35

Operators– use in sunflower (50 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL or AAOEL[a]**	**MoE[c] Repr**
	Work wear + gloves during M/L and A + RPE (FP1, P1 and similar) during M/L + drift reducing nozzles	0.0224	74.67	134
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + drift reducing nozzles	0.0099	33.00	303
	Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0159	53.00	189
	Soluble bags, Work wear + gloves during M/L + RPE (FP2, P2 and similar) during M/L + closed cabin	0.0071	23.64	423

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure).
(b): PPE: personal protective equipment; RPE: respiratory protective equipment.
(c): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure) or reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.

Table 8: Non-dietary exposure scenarios and margin of exposure (MoE) – workers

Worker – use in sunflower (50 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL[a]**	**MoE Repr[a]**
Short- to long-term exposure	Work wear	0.0006	2.73	5,000

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure); MoE: margin of exposure for carcinogenicity (ratio between critical systemic NOAEL and estimated exposure).

Table 9: Non-dietary exposure scenarios and margin of exposure (MoE) – residents

Resident – use in sunflower (50 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AOEL[a]**	**MoE[b] Repr**
All pathways – child	Buffer zone 2–3 m	0.0020	9.09	1,500
All pathways – adult		0.0006	2.73	5,000
All pathways – child	Buffer zone 10 m	0.0018	8.18	1,667
All pathways – adult		0.0006	2.73	5,000
All pathways – child	Buffer zone 10 m +	0.0017	7.73	1,765
All pathways – adult	Drift reduction nozzles 50%	0.0005	2.27	6,000

bw: body weight.
(a): AOEL: acceptable operator exposure level (short- to long-term exposure); AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure for carcinogenicity (for short- to long-term exposure), being the ratio between critical systemic NOAEL and estimated exposure.

Table 10: Non-dietary exposure scenarios and margin of exposure (MoE) – bystanders

Bystander – use in sunflower (50 g a.s./ha, 200 L/ha)				
EFSA model	**Risk mitigation measures**	**Systemic dose (mg/kg bw per day)**	**% AAOEL[a]**	**MoE[b] Repr**
Child: Spray drift	Buffer zone 2–3 m	0.0012	4.00	2,500
Vapour		0.0011	3.67	2,727
Surface deposits		0.0003	1.00	10,000
Entry in crops		0.0007	2.33	4,286
Adult: Spray drift	Buffer zone 2–3 m	0.0003	1.00	10,000
Vapour		0.0002	0.67	15,000
Surface deposits		0.0001	0.33	30,000
Entry in crops		0.0004	1.33	7,500
Child: Spray drift	Buffer zone 10 m	0.0007	2.33	4,286
Vapour		0.0011	3.67	2,727
Surface deposits		0.0001	0.33	30,000
Entry in crops		0.0007	2.33	4,286
Adult: Spray drift	Buffer zone 10 m	0.0001	0.33	30,000
Vapour		0.0002	0.67	15,000
Surface deposits		0.0000	0.00	163,339
Entry in crops		0.0004	1.33	7,500
Child: Spray drift	Buffer zone 10 m + Drift reduction nozzles 50%	0.0003	1.00	10,000
Vapour		0.0011	3.67	2,727
Surface deposits		0.0000	0.00	94,832
Entry in crops		0.0007	2.33	4,286
Adult: Spray drift	Buffer zone 10 m + Drift reduction nozzles 50%	0.0001	0.33	30,000
Vapour		0.0002	0.67	15,000
Surface deposits		0.0000	0.00	326,679
Entry in crops		0.0004	1.33	7,500

bw: body weight.
(a): AAOEL: acute AOEL (acute exposure), reference value used with the EFSA calculator for acute exposure.
(b): MoE: margin of exposure reproductive toxicity (for acute exposure), being the ratio between critical systemic NOAEL and estimated exposure.

2. Negligible exposure to non-target organisms (except humans)

The draft Technical Guidance on assessment of negligible exposure of an active substance in a plant protection product under realistic conditions of use (SANCO/2014/12096 (European Commission, 2015)) does not give any guidance for consideration of negligible exposure for non-target organisms except humans. Therefore, the assessment of potential negligible exposure to non-target organisms except humans was not assessed in this conclusion.

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FAO (Food and Agriculture Organization of the United Nations), 2015. Pesticide residues in food, Joint FAO/WHO Meeting on Pesticide Residues. Report 2015. FAO Plant Production and Protection Paper 223, 647 pp.

Abbreviations

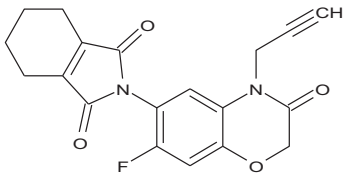
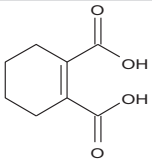
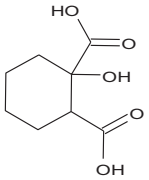
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
BBCH	growth stages of mono- and dicotyledonous plants
bw	body weight
DT_{90}	period required for 90% dissipation (define method of estimation)
EEC	European Economic Community
FAO	Food and Agriculture Organization of the United Nations
GAP	Good Agricultural Practice
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on 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)
LOQ	limit of quantification (determination)
M/L	mixing and loading
MRL	maximum residue level
NEU	northern Europe
NOAEL	no observed adverse effect level
OECD	Organisation for Economic Co-operation and Development
PAFF	Standing Committee on Plants, Animals, Food and Feed
PHI	preharvest interval
PPE	personal protective equipment
PRIMo	(EFSA) Pesticide Residues Intake Model
RAR	renewal assessment report
RMS	rapporteur Member State
RPE	respiratory protective equipment
SEU	southern Europe
SMILES	simplified molecular-input line-entry system
THPA	tetrahydrophthalic acid
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
WP	wettable powder
WHO	World Health Organization

Appendix A – List of representative uses evaluated for negligible exposure

Crop and/or situation[a]	Member state or country	Product name	F G or I[b]	Pests or group of pests controlled[c]	Formulation		Application				Application rate per treatment			PHI (days)[l]	Remarks[m]
					Type [d],[e],[f]	Conc. a.s.[i]	Method kind [f],[g],[h]	Growth stage and season[j]	Number min–max [k]	Interval between applications (min)	kg as/hL min–max	Water L/ha min–max	kg as/ha min–max		
Winter wheat	Northern Europe	Flumioxazin 50WP	F	Weeds	WP	500 g/kg	Spraying	Before 5th true leaf stage (up to BBCH 15)	1	–	0.005–0.015	200–600	0.03	–	
Sunflower	Northern and Southern Europe	Flumioxazin 50WP	F	Weeds	WP	500 g/kg	Spraying	Pre-emergence	1	–	0.0125–0.025	200–400	0.05	–	
Sunflower	Northern and Southern Europe	Flumioxazin 50WP	F	Weeds	WP	500 g/kg	Spraying	Post emergence BBCH 12-14 (2–4 leaves)	1	–	0.01–0.02	200–400	0.04	–	

(a): For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure).
(b): Outdoor or field use (F), glasshouse application (G) or indoor application (I).
(c): e.g. biting and suckling insects, soil born insects, foliar fungi, weeds.
(d): e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR).
(e): GCPF Codes - GIFAP Technical Monograph No 2, 1989.
(f): All abbreviations used must be explained.
(g): Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench.
(h): Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants – type of equipment used must be indicated.
(i): g/kg or g/L.
(j): Growth stage at 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.
(k): The minimum and maximum number of application possible under practical conditions of use must be provided.
(l): PHI: minimum preharvest interval.
(m): Remarks may include: Extent of use/economic importance/restrictions.

Appendix B – Used compound codes

Code/trivial name[a]	Chemical name/SMILES notation[b]	Structural formula[c]
flumioxazin	*N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-*yl*)cyclohex-1-ene-1,2-dicarboximide O=C1C=2CCCCC=2C(=O)N1c1cc2c(cc1F)OCC(=O)N2CC#C FOUWCSDKDDHKQP-UHFFFAOYSA-N	
tatrahydrophalic acid **THPA**	1-cyclohexene-1,2-dicarboxylic acid OC(=O)C=1CCCCC=1C(=O)O UFDHBDMSHIXOKF-UHFFFAOYSA-N	
1-OH-HPA-1	(1*RS*,2*RS;* 1*RS*,2*SR*)-1-hydroxy-1,2-cyclohexanedicarboxylic acid OC(=O)C1(O)CCCCC1C(=O)O SSBQOSIEGFXXEQ-UHFFFAOYSA-N	

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