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whether exposure of humans to flumioxazin can be considered negligible, taking into account the European Commission's draft guidance on this topic.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.

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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

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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 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. EFSA screened the 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-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 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 DT₉₀ 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 DT₉₀ 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.
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).

| Study | Uncertainty factor |
|-------|------------------|

**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                     |

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

bw: body weight.

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.

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| Study | Uncertainty factor |
|-------|------------------|

**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                     |

(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).

bw: body weight.

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

| EFSA model | Risk mitigation measures                                                                 | Systemic dose (mg/kg bw per day) | % AOEL or AAOEL<sup>(a)</sup> | MoE<sup>(c)</sup> |
|------------|------------------------------------------------------------------------------------------|----------------------------------|-------------------------------|-----------------|
| 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<sup>(b)</sup> | 0.0105                           | 47.73                         | 286             |
|            | Work wear + gloves and RPE (FP1, P1 and similar) during M/L and A<sup>(b)</sup>          | 0.0105                           | 47.73                         | 286             |
|            | Work wear + gloves during M/L and A + RPE (FP2, P2 and similar) during M/L<sup>(b)</sup> | 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<sup>(b)</sup> | 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<sup>(b)</sup> | 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

| EFSA model           | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL<sup>a</sup> | Repr<sup>a</sup> |
|----------------------|--------------------------|----------------------------------|---------------------|-----------------|
| 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

| EFSA model       | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL<sup>a</sup> | MoE<sup>b</sup> | 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

| EFSA model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AAOEL<sup>a</sup> | MoE<sup>b</sup> | Repr |
|------------|--------------------------|----------------------------------|---------------------|-----------------|------|
| Child:     | Spray drift              | Buffer zone 2–3 m                | 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:     | Spray drift              | Buffer zone 2–3 m                | 0.0002              | 0.67            | 15,000|
|            | Vapour                   |                                  | 0.0002              | 0.67            | 15,000|
|            | Surface deposits         |                                  | 0.0000              | 0.00            | 79,026|
|            | Entry in crops           |                                  | 0.0002              | 0.67            | 15,000|
| Child:     | Spray drift              | Buffer zone 10 m                 | 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:     | 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            | 272,232|
|            | Entry in crops           |                                  | 0.0002              | 0.67            | 15,000|
| Child:     | Spray drift              | Buffer zone 10 m + Drift         | 1.96E-04            | 0.65            | 15,306|
|            | reduction nozzles 50%    |                                  | 1.07E-03            | 3.57            | 2,804 |
|            | Vapour                   |                                  | 1.90E-05            | 0.06            | 157,895|
|            | Surface deposits         |                                  | 4.05E-04            | 1.35            | 7,407 |
|            | Entry in crops           |                                  |                     |                 |      |
### 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              | Buffer zone 10 m + Drift reduction nozzles 50% | 3.97E-05           | 0.13             | 75,567           |
|            | Vapour                   |                                  | 2.30E-04           | 0.77             | 13,043           |
|            | Surface deposits         |                                  | 5.51E-06           | 0.02             | 544,465          |
|            | Entry in crops           |                                  | 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) | Systemic dose (mg/kg bw per day) | % AOEL or AAOEL\(^{(a)}\) | MoE\(^{(c)}\) Repr |
|-----------------------------------------------------|---------------------------------|-----------------------------|-------------------|
| EFSA model                                          | Risk mitigation measures        |                             |                   |
| 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

| EFSA model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL(a) | MoE Repr(a) |
|------------|--------------------------|----------------------------------|-----------|-------------|
|            | Work wear                | 0.0006                           | 2.73      | 5,000       |

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.

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

| EFSA model | Risk mitigation measures | Systemic dose (mg/kg bw per day) | % AOEL(a) | MoE(b) Repr(b) |
|------------|--------------------------|----------------------------------|-----------|---------------|
| All pathways – child | Buffer zone 2–3 m | 0.0020 | 9.09 | 1,500 |
| All pathways – adult | Buffer zone 10 m | 0.0018 | 8.18 | 1,667 |
| 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.
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.

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

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

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**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<sub>90</sub>** 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
- **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<sup>(a)</sup> | Member state or country | Product name | F, G or I<sup>(b)</sup> | Pests or group of pests controlled<sup>(c)</sup> | Formulation | Application | Application rate per treatment | PHI (days)<sup>(l)</sup> | Remarks<sup>(m)</sup> |
|-----------------------------------|-------------------------|--------------|----------------|-----------------------------------------------|-------------|----------------|---------------------------------|-----------------|------------------|
| **Winter wheat**                  | Northern Europe         | Flumioxazin 50WP | F               | Weeds                                          | WP          | 500 g/kg       | Spraying Before 5th true leaf stage (up to BBCH 15) | 0.005–0.015 | 200–600 | 0.03 | |
| **Sunflower**                     | Northern and Southern Europe | Flumioxazin 50WP | F               | Weeds                                          | WP          | 500 g/kg       | Spraying Pre-emergence | 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) | 0.01–0.02 | 200–400 | 0.04 | |

<sup>(a)</sup>: 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).

<sup>(b)</sup>: Outdoor or field use (F), glasshouse application (G) or indoor application (I).

<sup>(c)</sup>: e.g. biting and sucking insects, soil born insects, foliar fungi, weeds.

<sup>(d)</sup>: e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR).

<sup>(e)</sup>: GCPF Codes - GIFAP Technical Monograph No 2, 1989.

<sup>(f)</sup>: All abbreviations used must be explained.

<sup>(g)</sup>: Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench.

<sup>(h)</sup>: Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants – type of equipment used must be indicated.

<sup>(i)</sup>: kg as/hL/min–max

<sup>(j)</sup>: 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.

<sup>(k)</sup>: The minimum and maximum number of application possible under practical conditions of use must be provided.

<sup>(l)</sup>: PHI: minimum preharvest interval.

<sup>(m)</sup>: Remarks may include: Extent of use/economic importance/restrictions.
### Appendix B – Used compound codes

| Code/trivial name<sup>(a)</sup> | Chemical name/SMILES notation<sup>(b)</sup> | Structural formula<sup>(c)</sup> |
|---------------------------------|---------------------------------------------|---------------------------------|
| **flumioxazin**                | \(N-(7\)-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2H-1,4-benzoxazin-6-y)cyclohex-1-ene-1,2-dicarboximide\) O=C1C=2CCCCC=2C(=O)N1c1cc2c(cc1F)OCC(=O)N2CC#C | ![Structural formula for flumioxazin](image) |
| **tetrahydrophalic acid THPA**  | 1-cyclohexene-1,2-dicarboxylic acid          | ![Structural formula for tetrahydrophalic acid THPA](image) |
| **1-OH-HPA-1**                 | \((1R\text{S},2R\text{S}; 1\text{RS},2\text{SR})\)-1-hydroxy-1,2-cyclohexanedicarboxylic acid\) O=C1(O)CCCCC1C(=O)O | ![Structural formula for 1-OH-HPA-1](image) |

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