Final Renewal report for the active substance zoxamide
finalised in the Standing Committee on Plants, Animals, Food and Feed
at its meeting on 23 March 2018
in view of the renewal of the approval of zoxamide as active substance
in accordance with Regulation (EC) No 1107/2009

1. Procedure followed for the re-evaluation process

This renewal report has been established as a result of the evaluation of zoxamide, in accordance with Regulation (EC) No 1107/2009\(^2\) and Commission Implementing Regulation (EU) No 844/2012\(^3\) following the submission of an application to renew the approval of this active substance expiring on 31 January 2019.


An application for renewal of the approval of zoxamide was submitted by Gowan Crop Protection Ltd in accordance with Article 1 of Regulation (EU) No 844/2012.

Commission Implementing Regulation (EU) 2018/84\(^6\) extended until 31 January 2019 the period of approval of zoxamide to allow the completion of its review.

Commission Implementing Regulation (EU) No 686/2012\(^7\) designated the rapporteur Member State and the co-rapporteur Member State which had to submit the relevant renewal assessment reports and recommendations to the European Food Safety Authority (EFSA).

For zoxamide the rapporteur Member State was Latvia and the co-rapporteur Member State was France.

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1. Renewal Report established in accordance with Art. 14 of Regulation (EU) No 844/2012; does not necessarily represent the views of the European Commission.
Latvia finalised in August 2016 its examination, in the form of a renewal assessment report. This Report was sent to the Commission and the European Food Safety Authority on 5 August 2016 and included a recommendation concerning the decision to be taken with regard to the renewal of the approval of zoxamide for the supported uses.

In accordance with Article 13 of Implementing Regulation (EU) No 844/2012, the EFSA organised an intensive consultation of technical experts from Member States, to review the renewal assessment report and the comments received thereon (peer review).

The EFSA sent to the Commission its conclusion on the risk assessment (Conclusions regarding the peer review of the pesticide risk assessment of the active substance)\(^8\) on 21 August 2017. This conclusion refers to background document A (final revised version of the renewal assessment report) and background document B (EFSA peer review report).

According to the provisions of Article 14 of Implementing Regulation (EU) No 844/2012, the Commission referred a draft renewal report on the renewal of approval to the Standing Committee on Plants, Animals, Food and Feed, for examination on 26 January 2018. The draft renewal report was finalized in the meeting of the Standing Committee on 23 March 2018.

The present renewal report contains the conclusions of the final examination by the Standing Committee. Given the importance of the conclusion of the EFSA, and the comments and clarifications submitted after the conclusion of the EFSA, these documents are also considered to be part of this renewal report.

2. Purposes of this renewal report

This renewal report, including the background documents and appendices hereto, has been developed and finalised in support of Commission Implementing Regulation (EU) 2018/692\(^9\) concerning the renewal of approval of zoxamide as active substance under Regulation (EC) No 1107/2009, and to assist the Member States in decisions on individual plant protection products containing zoxamide they have to take in accordance with the provisions of that Regulation, and in particular the provisions of Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EU) No 546/2011\(^10\).

This renewal report provides also for the evaluation required under part I, Section A.2(b) of the above mentioned uniform principles, as well as under several specific sections of chapter B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the requirements of Regulation (EU) No 283/2013\(^11\), submitted for the purpose of renewal of approval of the active substances, as well as the result of the evaluation of those data.

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\(^8\) EFSA (European Food Safety Authority), 2017. Conclusion on the peer review of the pesticide risk assessment of the active substance zoxamide EFSA Journal 2017;15(9):4980.


This renewal report will be made available to the public.

The information in this renewal report is, at least partly, based on information which is confidential and/or protected under the provisions of Regulation (EC) No 1107/2009. It is therefore recommended that this renewal report would not be accepted to support any registration outside the context of that Regulation, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this renewal report is based.


The overall conclusion from the evaluation is that it may be expected that plant protection products containing zoxamide will still fulfil the safety requirements laid down in Article 4(1) to (3) of Regulation (EC) No 1107/2009. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EU) No 546/2011, for each zoxamide containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses as a foliar applied fungicide on wine and table grapes and potatoes, which were proposed and supported by the applicant and mentioned in the list of uses supported by available data (attached as Appendix II to this review report).

The following reference values have been finalised as part of this evaluation:

ADI: 0.5 mg/kg bw per day,
ARfD: not allocated – not necessary,
AOEL: 0.3 mg/kg bw per day.

With particular regard to residues, the Theoretical Maximum Daily Intake (TMDI) according to EFSA PRIMO Model was not calculated by EFSA due to the outstanding data on the toxicity profile of the metabolites RH 141452 and RH 141455, on the nature of residues in processed commodities and on the magnitude of residues in potato tubers. However, the data available for these two metabolites indicate that: 1) they have no fungicidal activity; 2) their LD50 is > 5000 mg/kg bw; 3) metabolite RH 141455 is considered unlikely to be genotoxic (see also EFSA expert meeting) and results in an Ames test were negative for metabolite 141452; OECD QSAR Toolbox (version 3.4.0.17) analysis indicate that they are expected to have a lower toxicity than the parent compound zoxamide. Therefore, taking a conservative approach and using for these two metabolites the ADI value of 0.5 mg/kg bw/day of zoxamide, a provisionally estimated chronic assessment of RH 141452 and RH 141455 in potatoes can be performed: using the highest level of 0.11 mg/kg found for sum of RH-141455 (0.09 mg/kg) and RH-141452 (<0.02 mg/kg) in one of the trials, the TMDI values are estimated at max 0.1 % of the Acceptable Daily Intake (ADI), using the EFSA PRIMO Model rev.2A.

The calculation of the International Estimated Short-Term Intake (IESTI) is not needed because no Acute Reference Dose (ARfD) was considered necessary for zoxamide.

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements

All exposure estimates for operators and workers were below the Acceptable Operator Exposure Level (AOEL) without use of personal protective equipment (PPE). No Acute Acceptable Operator Exposure Level (AAOEL) was considered necessary.

The review has identified several acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

The following points were considered as a critical area of concern as reported in the EFSA Conclusions (2017) for zoxamide:

1. **The batches used in the (eco)toxicity studies were concluded as not being representative of both the old (existing) and the new applicants proposed technical specifications for the active substance** (see Sections 2 and 5).

   EFSA identified a critical area of concern because two impurities (RH-141288 and RH-149687) present in the new technical specification were not covered by the toxicological batches.

   However, the RMS does not agree with such conclusion. Impurity RH-141288 is also a significant mammalian metabolite (although found only in faeces in rat metabolism) and also an intermediate in the metabolic pathway which gives rise to other metabolites via oxidation. Therefore, it can be considered that RH-141288 has been intrinsically tested in the toxicity studies with the parent zoxamide. It is recommended that the Member States check the specifications of the technical material before granting authorizations and in case this impurity is present, a study to assess the toxicity of RH-141288 is requested from applicants and shared amongst Member States.

   Impurity RH-149687 is formed by hydrolysis of a chlorinating reagent used in the manufacture of zoxamide and has been extensively tested in a full range of toxicological studies which are in the public domain and which show that RH-149687 is not of toxicological concern.

The following points could not be finalised as reported in the EFSA Conclusions (2017) for zoxamide:

1. **The groundwater relevance assessment for groundwater metabolite RH-141455 predicted to be in annual average recharge leaving the top 1 m soil layer at > 0.75 μg/L could not be finalised, whilst the consumer risk assessment from drinking water originating from groundwater cannot be completed, as the available data are insufficient to set a reference value to complete the consumer risk assessment** (see Sections 2 and 4).

   The predicted concentrations of metabolite RH-141455 in groundwater are above 0.1 μg/L in all scenarios for grape vines and in all scenarios except the Sevilla scenario for potatoes (both under the PELMO and PEARL models and assuming applications are made every year or every three years). RH-141455 occurs at concentrations above 0.75 μg/L in four-five out of the nine pertinent FOCUS groundwater scenarios in both representative uses. EFSA therefore concludes that toxicological data are needed for this metabolite, e.g. a repeated-dose toxicity study, according to the guidance “Assessments of the relevance of metabolites in groundwater” (SANCO, 2003). However, considering the overall weight of evidence, RH-141455 should not be considered a relevant metabolite according to step 3 of the available guidance on metabolites in groundwater.
and is very unlikely to pose any risk to consumers via groundwater. The available data show that:
1) RH-141455 lacks the haloketone toxophore (chemical group responsible for the main toxicity) and was found to have no fungicidal activity.
2) The EFSA expert meeting concluded that RH-141455 is unlikely to be genotoxic and is less toxic than the parent compound zoxamide, which already shows a low toxic profile.
3) Predicted concentration levels of RH-141455 are below 0.75 μg/L in 3 scenarios for grape vines and in 5 scenarios for potatoes.
4) At the Pesticide Peer Review meeting, experts concluded that, if the approach of the Thresholds of Toxicological Concern (TTC) is used, RH-141455 would be of class Kramer 3 (i.e. exposure threshold would be 1.5 μg/Kg b.w). Using conservative assumptions, the estimated exposure would be 0.17 μg/Kg b.w, which is an order of magnitude lower than the appropriate TTC.
Since RH-141455 is considered less toxic than zoxamide, following a conservative approach, the ADI of zoxamide could be used to assess the consumer risk for RH-141455. Doing so, the predicted intake of RH-141455 from drinking water would result 0.17 μg/Kg (i.e. .0034% of the ADI for a 60 kg person). This means that RH-141455 would have to be significantly more toxic than zoxamide to pose any risk to the consumers via drinking water.

2. The human health and environmental risk assessment consequent to potential changes in the isomer composition for zoxamide and metabolites RH-127450, RH-163353, RH-150721 human health only] could not be finalised (see Sections 2, 3, 4 and 5).
For all of the substances assessed as racemic mixtures (zoxamide, RH-127450, RH-163353 and RH-150721), the chiral carbon is chemically stable, therefore interconversion is highly unlikely. Moreover, the available metabolism and degradation data do not show any preferential metabolism of one isomer over another one in either mammals, plants or the environment. A soil degradation study completed after the peer review showed no difference in rate of degradation of the isomers of neither zoxamide nor the major soil metabolite 127450. Even making the worst case assumption (all toxicity residues in one isomer and residues in crops comprised of only this isomer), dietary exposure would still be less than 8.2% the ADI.

3. The consumer risk assessment could not be finalised due to a number of data gaps that likely have an impact on the assessment of residue levels and due to the pending toxicological evaluation of metabolites which are included in the residue definition for risk assessment and monitoring (see Section 3).
EFSA concludes that a dietary consumer risk assessment could not be completed, due to data gaps on the toxicity profile of metabolites RH-141452, RH-141455 and RH-150721. EFSA proposes for some crops provisional residue definitions including some of these metabolites.
However, the overall evidence available as regards metabolites RH-141452, RH-141455 shows that they are unlikely to pose any risk to consumers via dietary exposure:
1) Both metabolites have no fungicidal activity.
2) LD50 for zoxamide as well as for both these metabolites is > 5000 mg/kg bw.
3) Data available show that RH-141455 is unlikely to be genotoxic and results in an Ames test were negative for metabolite 141452 and that they are both less toxic than the parent compound.

4) Using a conservative approach, the ADI of zoxamide could be applied to RH-141452 and RH-141455, and estimates using the EFSA PRIMO model rev 2.0 and based on provisionally estimated occurrence levels in potatoes result in exposure levels ranging from 0 to 0.1% of the ADI.

The metabolite RH-150721 is only relevant for the use on grapes, which has been excluded from the ‘supported uses’ (Appendix II).

Moreover, these data gaps were identified only late in the peer review (the current residue definition only comprises zoxamide). The applicant could provide them for renewal of product authorization, in accordance with the criteria for ‘category 4’ laid down in the guidance SANCO/2010/13170 rev.14.7 October 2016.

4. The consumer risk assessment from the consumption of drinking water could not be finalised, while satisfactory information was not available to address the effect of water treatment processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water (see Section 4).

This point cannot appropriately be addressed until agreed study guidelines or guidance is available. However, it can be mentioned that zoxamide does not contain any functional groups that could be precursors of nitrosamine. Moreover, considering the predicted environmental concentrations of zoxamide in surface water, it can be anticipated that the expected levels of degradation products reaching the water treatment plants would be much lower than 0.1 μg/L.

5. The chronic risk to earthworms could not be finalised for the active substance and all relevant soil metabolites except RH-141455 (Section 5).

The two studies available for assessing the chronic risk to earthworms were considered not valid by EFSA. However, the validity threshold for the “coefficient of variation in control” (30%) is not exceeded when results are compared to solvent controls rather than untreated controls. The studies can therefore be considered as valid. The type of soil used in the natural soil study is a recognised standard agricultural soil and represents a worst case due to its low carbon content: it is therefore appropriate to use this study to assess the chronic risk to earthworms from zoxamide.

However, the risk assessment based on the endpoints of these studies was still not acceptable and an additional study assessed at Member State level to refine the chronic risk to earthworms is considered necessary.

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4(3)(e) of Regulation (EC) No 1107/2009, provided that certain conditions are taken into account as detailed in section 6 of this report.
4. **Identity and Physical/chemical properties**

The main identity of zoxamide is given in Appendix I.

The active substance shall have a minimum purity of 953 g/kg.

5. **Endpoints and related information**

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 29(1) of Regulation (EC) No 1107/2009 and the uniform principles laid down in Regulation (EU) No 546/2011, the most important endpoints were identified during the re-evaluation process. These endpoints are listed in the conclusion of the EFSA.

6. **Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing zoxamide**

On the basis of the proposed and supported uses (as listed in Appendix II), the following issues have been identified as requiring particular and short term attention from all Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

– the protection of groundwater from metabolite RH-141455,
– the protection of bees, aquatic organisms and earthworms.

Conditions of use shall include risk mitigation measures, where appropriate.

7. **List of studies to be generated**

Further studies were identified which were at this stage considered necessary in relation to the approval of zoxamide under the current approval conditions.

The applicant shall submit confirmatory information as regards:

The effect of water treatment processes on the nature of residues present in drinking water.

The applicant shall submit the relevant information within two years of a guidance document on evaluation of the effect of water treatment processes on the nature of residues present in surface and groundwater is made public by the Commission.

Some endpoints however may require the generation or submission of additional studies to be submitted to the Member States in order to ensure authorisations for use under certain conditions. A complete list of studies to be generated, still ongoing or available but not peer reviewed can be found in the relevant part of the EFSA Conclusion (page 17).
8. **Information on studies with claimed data protection**

For information of any interested parties, the rapporteur Member State will keep available a document which gives information about the studies for which the applicant has claimed data protection and which during the re-evaluation process were considered as essential with a view to approval under Regulation (EC) No 1107/2009. This information is only given to facilitate the operation of the provisions of Article 62 of Regulation (EC) No 1107/2009 in the Member States. It is based on the best information available but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 62 of Regulation (EC) No 1107/2009 and neither does it commit the Commission.

9. **Updating of this renewal report**

The information in this report may require to be updated from time to time in order to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 13, 21, 38, 44, 56 of Regulation (EC) No 1107/2009. Any such adaptation will be finalised in the Standing Committee on Plants, Animals, Food and Feed, in connection with any amendment of the approval conditions for zoxamide.
APPENDIX I

Main identity

**ZOXAMIDE**

<table>
<thead>
<tr>
<th>Common name (ISO)</th>
<th>Zoxamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name (IUPAC)</td>
<td>(RS)-3,5-dichloro-N-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-p-toluamide</td>
</tr>
<tr>
<td>Chemical name (CA)</td>
<td>3,5-dichloro-N-(3-chloro-1-ethyl-1-methyl-2-oxopropyl)-4-methylbenzamide</td>
</tr>
<tr>
<td>CIPAC No</td>
<td>640</td>
</tr>
<tr>
<td>CAS No</td>
<td>156052-68-5</td>
</tr>
<tr>
<td>EC No (EINECS or ELINCS)</td>
<td>Not allocated</td>
</tr>
<tr>
<td>FAO SPECIFICATION</td>
<td>Not yet been established</td>
</tr>
<tr>
<td>Minimum purity</td>
<td>953 g/kg</td>
</tr>
<tr>
<td>Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured</td>
<td>Open</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{14}H_{16}NO_{2}Cl_{3}</td>
</tr>
<tr>
<td>Molecular mass</td>
<td>336.65 g/mol</td>
</tr>
<tr>
<td>Structural formula</td>
<td><img src="image-url" alt="Structural formula" /></td>
</tr>
</tbody>
</table>
### List of uses supported by available data

#### ZOXAMIDE

<table>
<thead>
<tr>
<th>Crop and/or situation (a)</th>
<th>Member State or Country</th>
<th>Product name</th>
<th>F/G or I (b)</th>
<th>Pests or Group of pests controlled (c)</th>
<th>Preparation</th>
<th>Application</th>
<th>Application rate per treatment</th>
<th>PHI (days) (m)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potato</td>
<td>NEU, CEU, SEU</td>
<td>Zoxium 240 SC</td>
<td>F</td>
<td>potato late blight <em>Phytophthora infestans</em></td>
<td>SC</td>
<td>broadc ast with spray boom</td>
<td>BBCH 20-80</td>
<td>0.018 kg a.s./L, min-max 1000 L/ha, min-max 0.180 kg a.s./ha, min-max 7 min</td>
<td>-</td>
</tr>
</tbody>
</table>

**Remarks:**

(a) For crops, the EU and Codex classifications (both) should be taken into account; where relevant, the use situation should be described (e.g., fumigation of a structure)
(b) Outdoor or field use (F), greenhouse application (G) or indoor application (I)
(c) *e.g.* biting and sucking insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(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 plant-

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**APPENDIX II**

List of uses supported by available data

**ZOXAMIDE**