Methoxyfenozide
SANTE/10295/2018 rev.3
13 December 2018

Final Renewal report for the active substance **Methoxyfenozide**
finalised in the Standing Committee on Plants, Animals, Food and Feed
at its meeting on 13 December 2018
in view of the renewal of the approval of **methoxyfenozide** as active substance
in accordance with Regulation (EC) No 1107/2009[1]

1. Procedure followed for the re-evaluation process

This renewal report has been established as a result of the evaluation of methoxyfenozide, 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 in March 2015.

Methoxyfenozide is a substance that was included in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market, by Commission Directive 2005/3/EEC[4]. Methoxyfenozide is deemed to have been approved under Regulation (EC) No 1107/2009 and is listed in Part A of the Annex to Commission Implementing Regulation (EU) No 540/2011[5].

An application for renewal of the approval of methoxyfenozide was submitted by Dow Agro-science Iberica in accordance with Article 1 of Regulation No. 844/2012.

Commission Implementing Regulation (EU) 2017/841[6] extended until 31 July 2018 the period of approval of methoxyfenozide to allow the completion of its renewal assessment.

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

For methoxyfenozide the rapporteur Member State was the United Kingdom and the co-rapporteur Member State was Slovakia.

---

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.
2 OJ L 309, 24.11.2009, p. 1.
3 OJ L 252, 19.9.2012, p. 26.
4 OJ L 20, 22.1.2005 p.19.
5 OJ L 153, 11.6.2011, p. 1.
6 OJ L 125, 18.5.2017, p. 12.
7 OJ L 200, 27.7.2012, p. 5.

The United Kingdom 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 4 August 2016 and included a recommendation concerning the decision to be taken with regard to the renewal of the approval of methoxyfenozide 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 10 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 25 May 2018. The draft renewal report was finalised in the meeting of the Standing Committee on 13 December 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) 2019/158**[9] concerning the renewal of approval of methoxyfenozide as active substance under Regulation (EC) No 1107/2009, and to assist the Member States in decisions on individual plant protection products containing methoxyfenozide 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.

This renewal report will be made available to the public.

---

8 EFSA (European Food Safety Authority), 2017. Conclusion on the peer review of the pesticide risk assessment of the active substance methoxyfenozide EFSA Journal 2017;15(9):4978.

9 OJ L 31, 1.2.2019, p. 21.

10 OJ L 155, 11.6.2011, p. 127.

11 Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance (OJ L 93, 3.4.2013, p. 1).

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.

3. Overall conclusion in the context of Regulation (EC) No 1107/2009

The overall conclusion from the evaluation is that it may be expected that plant protection products containing methoxyfenozide 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 methoxyfenozide 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 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 renewal report). Not all initially proposed uses are included in Appendix II because the data submitted were not sufficient to conclude on a safe use due to the lack of data in several areas of the assessment and potential risk for groundwater contamination. Therefore, the renewal of the substance is restricted to the safe uses identified in greenhouse.

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

ADI: 0.1 mg/kg bw per day (confirming the value previously set in 2004),
ARfD: 0.1 mg/kg bw (changing the value previously set which was 0,2 in 2004),
AOEL: 0.06 mg/kg bw per day (changing value previously set which was 0,1 in 2004),
AAOEL: 0.06 mg/kg bw per day (new value).

With particular regard to residues, on the basis of a provisional consumer risk assessment based on the parent compound, the Theoretical Maximum Daily Intake (TMDI) for all considered consumer groups is around 4 % of the Acceptable Daily Intake (ADI), based on EFSA PRIMO Model rev.2A and worst case International Estimated Short-Term Intake (IESTI) is 70% of the Acute Reference Dose (ARfD) for lettuce.

All evaluations were below the AOEL without use of personal protective equipment (PPE).

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 of Article 29(1) of Regulation (EC) No 1107/2009 and of the uniform principles laid down in Regulation (EU) No 546/2011.

The review has identified acceptable exposure scenarios for operators, workers, residents, 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 could not be finalised or were considered as a critical area of concern as reported in the EFSA Conclusions (2017) for methoxyfenozide:

Issue which could not be finalised

1. *The need for further tests and risk assessment to unique human metabolites could not be finalised whilst an in vitro comparative metabolism study was not submitted*

   This data gap is related to the new data requirement under Regulation (EU) 283/2013 which has not been fulfilled by the applicant but its absence has not been identified in an earlier phase of assessment.

   To note that livestock metabolism studies available were covered by the mammalian toxicology studies. Moreover, considering an agreed guidance for the evaluation of results deriving from such type of study is not yet available, it is considered proportionate to allow for a later submission of the study as confirmatory information (see section 7 of this report).

2. *Methoxyfenozide does not meet the interim criteria for endocrine disruption. With regard to the scientific risk assessment, a conclusion on whether thyroid toxicity effects in rats could be endocrine-mediated could not be finalised*

   The majority of experts in the peer review concluded on a data gap with respect to mechanistic data investigating whether thyroid toxicity effects in rats might be endocrine mediated and relevant to humans (level 2 and level 3 studies according to OECD conceptual framework). However, the RMS does not agree with this conclusion and considers them secondary effects on the endocrine system due to induction of hepatic enzymes. In addition, no substance-related adverse effects at the top dose were detected on another carcinogenicity study on mouse, and no substance-related adverse reproductive effects at the top dose were detected in the two generation rat study and in the developmental toxicity study in rat and rabbit.

   As regards non-target organisms, it is unlikely that methoxyfenozide is an endocrine disrupter via the estrogenic, androgenic and steroidogenic modalities. Additionally, an amphibian metamorphosis assay did not provide any evidence of endocrine activity or potential endocrine related effects via the thyroid modality. It can therefore be concluded that methoxyfenozide is unlikely to be an endocrine disruptor.

   Based on this information the new criteria to identify endocrine disrupting properties set in Commission Regulation (EU) 2018/605[12], which became applicable the 10 November 2018, are unlikely to be fulfilled because 1) it is unlikely that methoxyfenozide is an endocrine disrupter via the estrogenic, androgenic and steroidogenic modalities and 2) available evidence (amphibian metamorphosis assay) indicates that methoxyfenozide is unlikely to show thyroid endocrine activity.

   However, it is considered proportionate to request the applicant to provide further information to confirm the absence of thyroid endocrine activity in order to increase the confidence in this conclusion. (see section 7 of this report).

[12] Commission Regulation (EU) 2018/605 of 19 April 2018 amending Annex II to Regulation (EC) No 1107/2009 by setting out scientific criteria for the determination of endocrine disrupting properties. (OJ L 101, 20.4.2018, p. 33).

3. *The consumer dietary risk assessment is regarded as not finalised for the products of plant and animal origin and drinking water in relation with drinking water treatment products.*

The consumer risk assessment could not be finalised mainly for data missing in rotational crops and livestock exposure. However, taking into account the results of the provisional consumer risk assessment, based on the residues definition of sole parent compound, it is shown a wide margin of safety, with consumer exposure in the worst case less than 4% of the ADI and no exceedance of the ARfD with worst case lettuce 70% ARfD calculated using the EFSA Primo v2 model. In addition, focusing on the tests results concerning supported uses on fruiting vegetables, the information available is judged sufficient to derive MRLs proposal. With respect to the water treatment processes, and their potential effect on the nature of residues present in water, in the absence of specific guidance available to address this issue, it is considered appropriate and consistent with other decisions taken, to require confirmatory information to be submitted when guidance at EU level will be available (see section 7 of this report).

4. *The risk assessment for honeybees (chronic adult and larvae) for methoxyfenozide could not be finalised*

Methoxyfenozide shows low acute toxicity to honeybees via oral and contact route. Semi-field and fields studies have been submitted (including two brood feeding tests) but they were not considered reliable in peer review to conclude upon for identified shortcomings. However, some of the studies were recommended by experts to be used as appropriate additional information and their outcomes were positive with no adverse effect on honey bee brood and adults. The RMS considers also that the results do confirm the original conclusions of absence of unacceptable risk. Moreover, focusing on the supported use on fruiting vegetables in confined space of greenhouse and through only one application, the exposure to honeybees should be very limited for the inaccessibility indoor and further data could be submitted in phase of re-assessment and potential re-registration of plant protection products containing methoxyfenozide.

5. *The risk assessment for non-target arthropods for methoxyfenozide could not be finalised*

The substance is an insect growth regulator (IGR) acting on moulting against some Lepidoptera species so the standard risk assessment is considered not relevant because it does not cover the relevant route of exposure and the sensitive life stages. When originally assessed on the basis of standards test species it was concluded risk for non-target arthropods to be acceptable. A field study is available but it was considered not robust enough and experts agreed further information is needed to address the risk to non-target arthropods in-field and off-field, particularly for Lepidoptera, the risk off-field should be addressed. However, considering the outcomes of the studies submitted and the restriction of approval to indoor uses, it is proportionate to allow the completion of risk assessment for non-target arthropods in phase of re-assessment and potential re-registration of plant protection products containing methoxyfenozide.

6. *The risk assessment for sediment dwellers for methoxyfenozide could not be finalised*

The results of the assessment of a mesocosm study resulted for methoxyfenozide in one safe scenario in case of fruiting vegetables outdoor, all scenarios safe for vine and most for maize, and leafy vegetables. Moreover, EFSA conclusions report that toxicity data were

available for the pertinent surface water and sediment metabolite M08 and M14 and using these data a low risk for *Chironomus* riparius was identified for all representative uses.

To note also that the results of studies on other soil organisms show a wide margin of safety with respect to methoxyfenozide.

Given the renewal will be limited to indoor uses in line with Guidance SANCO/10329/2002 rev.2, it is considered proportionate to allow submission of further data to complete the risk assessment at national level with data concerning exposure in the sediment to finalise the risk assessment to sediment dwellers (spiked sediment study).

Critical area of concern

7) Potential ground water contamination above the parametric drinking water limit of 0.1 lg/L by methoxyfenozide and toxicological relevant metabolite RH131154 (M08)

With respect to methoxyfenozide the evaluation under PEARL Focus Model resulted in one scenario below the trigger value of 0,1 ug/L for maize, tomato and cabbage. Using PELMO model 3 scenarios are safe for vines and 1 for all other crops, to note other scenarios are ranging up to a maximum of 0,515 ug/L.

With respect to the major metabolite M08 in both PEARL and PELMO Models there is no scenario below the limit of 0,1 ug/L and values are ranging from 0,487 up to max value of 7,478 ug/L. It should be noted that this result is also deriving from the use of a conservative DT50 default value of 1000 days in peer review, while the results from the original DRAR would have identified 3 safe Focus scenarios.

Considering the fruiting vegetables in greenhouse, the results of assessment performed for potential groundwater contamination for the parent compound and major metabolite M08 are positive leading to values below the limit of 0,1 ug/L. Therefore, the use to fruiting vegetables indoor will not lead to unacceptable effects.

Given that methoxyfenozide fulfils the criteria as persistent (P) and toxic (T) in accordance with the criteria provided for in points 3.7.2.1 and 3.7.2.3 of Annex II to Regulation (EC) No 1107/2009 respectively, it meets the conditions of indent 2 of point 4 of Annex II and therefore shall be re-approved pursuant to Article 24 of Regulation (EC) No 1107/2009 as a candidate for substitution.

4. Identity and Physical/chemical properties

The main identity of methoxyfenozide is given in Appendix I.

The active substance shall have a minimum purity of 970 g/kg.

The review has established that for the active substance the impurities RH-116267 and ter-butylhydrazine are of toxicological concern and must not exceed maximum levels of 2 g/kg and 0,001 g/kg respectively in the technical material.

5. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorizations, 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 authorizations of plant protection products containing methoxyfenozide

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:

- Only uses in greenhouses may be authorised.

Member States must pay particular attention to:

- the protection of groundwater, when the substance is applied in regions with vulnerable soil and/or climatic conditions;
- the risk of accumulation in soil;
- the protection of non-target arthropods, sediment dwelling and aquatic organisms.

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 methoxyfenozide under the current approval conditions.

The applicant shall submit to the Commission, the Member States and the Authority confirmatory information as regards:

(1) a comparative in vitro metabolism study on methoxyfenozide;
(2) the effect of water treatment processes on the nature of residues present in surface and groundwater, when surface water or groundwater is abstracted for drinking water.

The applicant shall submit to the Commission, the Member States and the Authority the information referred to in point 1 by 1 April 2020 and in point 2 within 2 years after adoption of a guidance document on evaluation of the effect of water treatment processes on the nature of residues present in surface and groundwater.

The applicant shall also provide an updated assessment including, where relevant, further information to confirm the absence of thyroid endocrine activity in accordance with Points 3.6.5 and 3.8.2 of Annex II of Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 by 1 February 2021.

Some other endpoints however may require the generation or submission of additional studies to be submitted to the Member States in order to ensure authorizations 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 Conclusions (pag.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.

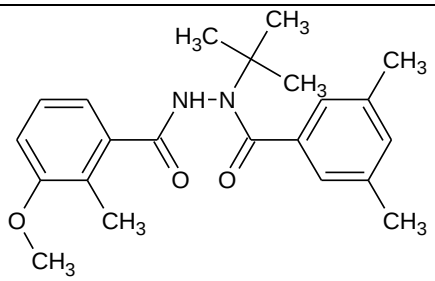
9. Updating of this renewal report

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 methoxyfenozide.

APPENDIX I

Main identity

METHOXYFENOZIDE

Common name (ISO)	Methoxyfenozide
Chemical name (IUPAC)	*N-tert*-butyl- *N'*-(3-methoxy-*o*-toluoyl)-3,5-xylohydrazide
Chemical name (CA)	3-methoxy-2-methylbenzoic acid 2-(3,5-dimethylbenzoyl)-2-(1,1-dimethylethyl)hydrazide
CIPAC No	656
CAS No	161050-58-4
EC No (EINECS or ELINCS)	605-245-2
FAO SPECIFICATION	None
Minimum purity	970 g/kg
Identity of relevant impurities (of toxicological, ecotoxicological and/or environmental concern) in the active substance as manufactured	Tert-butylhydrazine at level <0.001 g/kg RH-116267 at level < 2 g/kg
Molecular formula	$C_{22}H_{28}N_2O_3$
Molecular mass	368.47 g/mol
Structural formula	

APPENDIX II

List of uses supported by available data

METHOXYFENOZIDE

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)	Remarks:
					type (d-f)	conc. of as (i)	method kind (f-h)	growth stage & season (j)	number max (k)	interval between appl. (min)	L Product/ ha max	water L/ha min-max	g as/ha max	(l)	(m)
Fruiting vegetables – *Solanaceae* – Tomatoes, Peppers, Aubergines	EU	GF-837	G	SPODSP, loopers, PYRUNU, HELIAR	SC	240	Broadcast Foliar	BBCH 51-87 Feb to Nov	1	NA	6.4 - 72	200 - 1500	96 - 144	1	

Remarks:

(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 sucking 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 applications possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions