Committee for Risk Assessment

RAC

Annex 2
Response to comments document (RCOM) to the Opinion proposing harmonised classification and labelling at EU level of

azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate

EC Number: -
CAS Number: 131860-33-8

CLH-O-0000001412-86-206/F

Adopted

8 June 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON AZOXYSTROBIN (ISO); METHYL (*E*)-2-{2-[6-(2-CYANOPHENOXY)PYRIMIDIN-4-YLOXY]PHENYL}-3-METHOXYACRYLATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: azoxystrobin (ISO); methyl (*E*)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate
EC number: -
CAS number: 131860-33-8
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.10.2017	Germany	Lanxess Deutschland GmbH	Company-Downstream user	1
Comment received				
2.2 Identified uses (page 15) A minor point but the representative use on kale was representative of the leafy brassica crop group and not just kale.				
Dossier Submitter's Response				
Thank you for your comment, this is noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	2
Comment received				
Identity of the active substance: - p. 4, Table 1 and p. 12, Table 6: According to the data submitted in the frame of the approval of azoxystrobin under Reg. (EU) 1107/2009, the minimum purity of the substance is 96.5% and the maximum contents of the relevant impurities z-isomer and toluene are 7 g/kg and 2 g/kg respectively. Nevertheless, the regulation Reg.703/2011 approving the active substance azoxystrobin, in accordance with Regulation (EC) No 1107/2009 referred to 930 g/kg for the active substance, 25 g/kg for the z-isomer and 2 g/kg for toluene. - p. 11, Table 4: An inversion was done between molecular formula and molecular weight range				

- p. 12, Table 5: According to the data submitted in the frame of the approval of azoxystrobin under Reg. (EU) 1107/2009 the concentration range is 97.27 – 98.47%. Please clarify those points.

Dossier Submitter's Response

Thank you for your comments. We note that the molecular weight and formula have been presented in the wrong rows of table 4.

Regarding the purity/impurities, the information in the CLH report took account of the information submitted in the frame of 1107/2009 and the original Competent Authority Report (CAR) submitted to ECHA for the evaluation according to Regulation (EU) No 528/2012. It is our understanding that the minimum purity should be ≥ 96.5% and the content of the relevant impurities should be ≤ 0.7% Z-isomer and ≤0.2% toluene. In any case, the impurities do not impact on the proposed classification.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	3

Comment received

Substance ID:
In the Competent Authority Report (CAR) for the evaluation of active substances according to Regulation (EU) No 528/2012 chapter 3.1 Identity of the active substance, toluene is given as a relevant impurity having a concentration of max 0.2% w/w. However, in the CLH report as well as in the IUCLID file a concentration of <0.5% w/w was presented. Please clarify which concentration is correct or why there is a difference in the concentrations within the different documents.

Mutagenicity:
During the BPR procedure, Germany indicated concern due to the genotoxic potential of azoxystrobin. Unfortunately, the endpoint genotoxicity was not addressed in this CLH dossier. Please find below a comment on the discussion in the "Extract from the Assessment Report (May 2009) prepared by RMS UK in the context of Annex I renewal under the PPP directive" which is annexed to this comment. Azoxystrobin was also assessed as biocidal active substance. Documentation should be available in R4PB.

DE considers that the toxicological information provided for Azoxystrobin in the Assessment Report (May 2009) prepared by RMS UK in the context of Annex I renewal under the PPP directive was insufficient to conclude that the substance is not genotoxic in vivo.
While Azoxystrobin was negative in the bacterial mutagenicity test, positive responses were observed in the in vitro mammalian cell gene mutation test (OECD TG 476) and the in vitro mammalian chromosome aberration test (OECD TG 473). The detection of chromosome aberrations together with the observation of small mutant colonies in the gene mutation assay indicated a clastogenic mode of action. These experimental results were in agreement with structure-activity relationships as predicted in silico using Toxtree software.

For Azoxystrobin, an in vivo UDS assay in the rat and a mouse micronucleus were available.
• The UDS test cannot be regarded as an appropriate study. As an indirect indicator test

for DNA damage, the UDS assay responds to mutagens reacting with DNA (e.g. bulky adducts) triggering nucleotide excision repair. Therefore, the UDS test is considered as an adequate follow-up test for substances that are positive in the bacterial mutagenicity tests, yet not for clastogenic substances (see also OECD TG 486 and EFSA Scientific Committee: draft Scientific opinion for the "Reflection on interpretation of some aspects related to genotixicity assessment"). • The micronucleus test in vivo did not meet the requirements of the current OECD TG and can thus not be regarded as acceptable. Among other deficiencies, only one dose was used which hampers the evaluation of dose-response. Furthermore, it remained unclear whether the bone marrow being the target was reached by the test compound as the reduction in the proportion of polychromatic to normochromatic erythrocytes was not evident after 24h. Thus, DE considers the genotoxicity data provided as insufficient to exclude a genotoxic potential of Azoxystrobin with sufficient certainty. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Azoxystrobin_AR_08_Vol3_B6_part1_(May_2009)_public.pdf
Dossier Submitter's Response
Thank you for your comments. Substance ID: The information in the CLH report took account of the information submitted in the frame of 1107/2009 and the original Competent Authority Report (CAR) for the evaluation according to Regulation (EU) No 528/2012. It is our understanding that the maximum content of toluene should be 0.2% and not 0.5% as noted in the CLH report. However, in either case, this impurity does not impact on the proposed classification. Mutagenicity: Thank you for your comments, however the proposal is targeted to the removal of the * and a consideration of the environmental data. We are not able to update the CLH report at this stage.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
23.10.2017	Germany	Lanxess Deutschland GmbH	Company-Downstream user	4
Comment received				
5.1.1 Environmental hazard assessment (stability) (page 23) It states 'Unidentified degradates accounted for up to 30% applied radioactivity and consisted of at least 7 discrete bands' - we would like it noting that no single unknown was present at >7.8%.				
Dossier Submitter's Response				
Thank you for the comment, this is noted. However, we are not able to update the report at this stage.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	5
Comment received				
FR agrees with the proposed classification. Nevertheless, FR disagrees with the ATE proposed. Indeed, according to the raw data, CL50 seems to be between 511 and 767 µg/L. In a conservative approach, a value of 511 µg/L can be used for CL50. Therefore, FR proposes to set the ATE at 0.5 mg/L instead of 0.7 mg/L.				
Dossier Submitter's Response				
Thank you for your comments and support for the proposed classification. Justification for the ATE is provided in the CLH report, but we note your comments and suggest that this is considered by RAC.				
RAC's response				
The ATE is derived from the LC_{50} where available. In this study the LC_{50} for males was calculated at 0.962 mg/l and at 0.698 (0.70) mg/l for females. The proposed ATE of 0.7 mg/l is essentially the lowest LC_{50} estimated from the data and considered sufficiently conservative by the RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	6
Comment received				
Based on the presented data, the proposal to classify Azoxystrobin into Acute tox 3 (H331) with an ATE of 0.7 mg/L is supported. The proposed ATE value is missing in table 2 in the report. It should be part of the entry in Annex VI. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Azoxystrobin_AR_08_Vol3_B6_part1_(May_2009)_public.pdf				
Dossier Submitter's Response				
Thank you for your support. We note that the ATE value is missing from table 2.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2017	Spain		MemberState	7
Comment received				
In an acute inhalation study in rats, the LC50 of azoxystrobin was found to be 0.698 mg/l in females and 0.962 mg/l in males. Therefore, the criteria for classification as Acute Tox 3; H331 – Toxic if inhaled are met; confirming the existing classification. Therefore, we agree with the dossier submitter that the * should be removed from the existing Annex VI of CLP entry. We also see appropriate to include an ATE value of 0.7 mg/l, based on the lowest LC50 reported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
23.10.2017	Germany	Lanxess Deutschland GmbH	Company-Downstream user	8
Comment received				
5.1.1 Environmental hazard assessment (stability) (page 23) It states 'Unidentified degradates accounted for up to 30% applied radioactivity and consisted of at least 7 discrete bands' - we would like it noting that no single unknown was present at >7.8%.				
Dossier Submitter's Response				
Thank you. We are not able to update the report at this stage but note your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	9
Comment received				
FR agrees with the classification, the acute and the chronic M factors proposed for Environmental hazards.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium		MemberState	10
Comment received				
Based on the results of the available aquatic acute toxicity test on the most sensitive species Americamysis bahia (96hEC50=0.055 mg/l, 28NOEC=0.00954mg/l), the fact that the substance is non rapidly degradable BE CA considers it justified to classify azoxystrobin, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. In view of the proposed classification and toxicity bands for aquatic toxicity, an M-factor for acute toxicity of 10 (EC50 between 0.01 mg/l and 0.1 mg/l) and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and NOEC between 0.001 and 0.01mg/l) can be assigned. BE CA agrees with the proposed M-factors.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Finland		MemberState	11
Comment received				
According to mysid shrimp studies considered valid for classification purpose of the toxicity of azoxystrobin, the acute EC50 value is between 10-100 µg/l and the chronic NOEC value is between 1-10 µg/l. Furthermore, the substance is not considered rapidly degradable and predicted to have a low bioaccumulation potential. Based on the available information FI CA supports the proposed classification of Aquatic Acute 1 with M-factor of 10 and Aquatic Chronic 1 with M-factor of 10 for azoxystrobin.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	12
Comment received				
We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) and the acute/chronic with M-factors of 10. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Azoxystrobin_AR_08_Vol3_B6_part1_(May_2009)_public.pdf				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Azoxystrobin_AR_08_Vol3_B6_part1_(May_2009)_public.pdf [Please refer to comment No. 3, 6, 12]